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GTF21 and positive emotionality in preschool children

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Liquid poison for children in every supermarket

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Colophon

The Erasmus Journal of Medicine (EJM) is a scientific magazine by and for students, especially students of Erasmus MC University Medical Center Rotterdam. It was initiated by the MFVR (the medical students' organization of Erasmus MC). The journal appears twice a year. It is published on paper (1500 copies) and on the EJM website (www.erasmusjournalofmedicine.nl).

The main purpose of the EJM is to encourage medical and research master students to conduct research (empirical studies or systematic reviews) and report on this research, and become acquainted with a professional publishing process either as authors, reviewers or editors. A secondary purpose is to make the results of excellent student-driven research known to others.

The journal contains articles describing original research, systematic reviews, extended abstracts (summaries of recently conducted studies), calls from research projects for students to participate, opinion papers written by students, editorial comments, case reports, clinical lessons, clinical images, and letters to the editor.

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Foreword

Five years Erasmus Journal of Medicine

It is with great pride that I congratulate the editors of Erasmus Journal of Medicine on their fifth anniversary. When Erasmus MC started its own scientific journal five years ago, the ambitions were high. Now, looking back on all the issues of the journal, the editors can be satisfied. The expectations have been met. The quality of the articles, written by our medical students, has been high right from the start and has continued to be so.

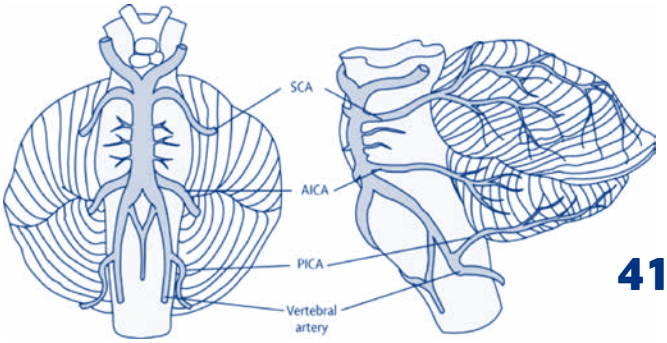
Our university medical center excels in translational and clinical research. We do not just develop scientific knowledge, we also introduce it and study its clinical effects and effects in society as a whole. Our work in this continuum of scientific research puts us in the top ten of best medical institutes in Europe (QS World University Ranking 2014). It also makes our researchers successful in the European Research Area, which is becoming increasingly important for effective collaboration and funding. Erasmus MC has been a partner in 165 Framework Program 7 (FP7) projects of the European Commission and is hosting 18 European Research Council (ERC) grantees. The first projects within Horizon2020, which is the successor of FP7, have already been signed.

For me as the Dean of Erasmus MC, it is an incredibly encouraging thought that Erasmus Journal of Medicine offers our medical students the opportunity to make their first steps as biomedical researchers. As teachers at Erasmus MC, we are convinced that scientific training is a valuable asset for young professionals who will be working in medical practice within a few years.

A perfect occasion to share our pride was the public event 'In Praise of Medicine' last October at Congress Centerl De Doelen in Rotterdam. After fascinating lectures by Nobel laureate Carol Greider and Erasmus MC speaker Stefan Sleijfer, which both linked fundamental and clinical research, the Erasmus MC fellowships were awarded to young researchers. Yet another highlight was the award for the best article in Erasmus Journal of Medicine 2014 presented to Emma van der Ende and her co-authors for their article 'Diagnostic value of FDG-PET/CET in fever of unknown origin'. A true celebration of talent.

Prof.Dr. Jaap Verweij,
Dean and vice-chairman of the Executive Board of Erasmus MC

Erasmus Journal of Medicine



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EJM: Consolidation and Grow

The latest developments of Erasmus Journal of Medicine can be described using two words: Consolidation and grow. Consolidation by realizing new challenges such as the KNMG-EJM grant and research master prizes; all initiatives to encourage a broad spectrum of medical students and research masters to contribute to EJM and further develop their scientificskills. EJM, in association with KNMG district VI, presents an award of €5.000,- for the best research proposal submitted by a medical student. We would appreciate it very much, if papers resulting from this research would be published in EJM as research papers. In this way, we intend not only to train medical students in scientific writing but also in grant writing and becoming research-oriented doctors. Consolidation by pushing the boundaries towards Medical Delta. Research driven life sciences and medical technology are now playing a critical role in the future understanding of what we call medicine and science now. We have set up extensive network collaborations with Nanobiology, Clinical Technology and Medical Engineering and aim to publish the first results of these fruitful collaborations in the next issue of EJM. During the "Lof der Geneeskunst" , the best paper published in EJM and selected by our scientific jury has been awarded by the Dean of Erasmus MC, prof dr Verweij (EJM award) which will be an annually recurring phenomenon.

The presented journal is the product of the hard work delivered by many; our student and staff editors and external reviewers. Again, we present an issue with a variable content including papers in the following sections: systematic reviews, opinion papers, research articles and case reports. We hope that also this issue will stimulate students to write and submit their work to us.

On national level, we are recognized as an established student oriented educational journal. We were pleased to guide our colleagues from Radboud Medical University in Nijmegen and UMCG in Groningen to set up a similar medical journal. Our aim and ambition is to develop international recognition in the future.

More deepening, exploring and extension of all our educational activities with a clear growing image is the hall mark of the editorial 2014. I invite you to read this eight edition of EJM and share with us your feedback, ideas for new skills and abilities to learn from.

Ajda T Rowshani, MD, PhD
Internist, Chair of the editorial board
Rotterdam, January 2015, ejm@erasmusmc.nl

Fresh research ideas and fresh members wanted!

Research plays an essential role within the medical field as nowadays we all need to work 'evidence based'. Knowing this, many students are taking advantage of the possibilities to become involved in research or even start their own projects. The Erasmus MC also offers five different Research Masters that are aimed at educating students to also become good researchers. Besides, a lot of departments are looking for bachelor students to assist ongoing clinical studies. These are convenient ways for students to obtain abilities that are crucial in clinical practice and necessary for the development of future physicians.

However, some students find it difficult to join a research project or do not know how to accomplish their own research ideas. This is unfortunate since students may have brilliant fresh research ideas. Therefore, we decided to remedy this obstacle. That is to say, we are giving students an exceptional opportunity to make a start with their very own project. The competition for the KNMG-EJM Grant, including a €5.000,-budget, has started and the prize will be given to the student with the best research proposal. More information can be found further in this journal.

In this issue, you can also find an advertorial for the ISCOMS congress in Groningen, which is a good opportunity for students to discuss their study results and further research proposals, while broadening their social networks under a good company.

Finally, we welcome a fresh member of the Student Editorial Board of the EJM, Begum Pekbay, second year's medical student. She decided to join the EJM as a Student Reviewer during her first study year and it was for her the ideal opportunity to develop reading and writing skills. Being a student editor means enjoying a strong teamwork between students, physicians and investigators aiming to publish another great EJM issue. The EJM is a unique journal since it is designed by students for students, which emphasizes the continuous urge for academic development at our medical school. Thus, if you also prefer to expand your scientific skills regardless your academic year, do not hesitate and apply to the EJM because we are still looking for new student editors!

So do not waste any more time and grab these opportunities to discover the world of research!

Student editors: Fatih Incekara, Mostafa Mohseni, Sandrine Nugteren Begum Pekbay, Iris van der Sar

Prohibition of energy drinks; how far can we go?

The article of Ranjit Singh entitled "Liquid poison for children, for sale in every supermarket" in the current issue of the EJM addresses the increasing treat of energy drink consumption especially among young people. Singh argues that the Dutch government should, like they already did for alcohol and tobacco, instate a minimum age for the sale of energy drinks. According to the author, youngsters and especially children are today victims of misleading advertisement from major energy drink companies. Children need to be protected by the Government because they are not capable of making an autonomous decision. The terms youngsters and children are both used by the author for the same purpose, which might cause some confusion.

However, in my opinion we have to be careful in the prohibition of energy drinks, despite its underestimated bad health outcomes such as caffeine intoxication. The toxic threshold of caffeine is around 400mg/day for adults, 100mg/day for adolescents (12-18 years) and 2.5mg/kg/day for children (<12years) [1]. A can of 250 ml energy drink contains around 80mg of caffeine. This means that one can of energy drink almost reaches the toxic threshold for adolescents. Symptoms of caffeine intoxication include irritability, insomnia, tachycardia, palpitations and nervousness [1].

The main question is whether the risk of caffeine intoxication justifies a restriction on youngsters from buying energy drinks? The answer to this question is complicated and will raise questions whether other drinks, which also contain high doses of caffeine such as cola, tea and coffee, should be prohibited too. Such a prohibition might lead to a certain anxiety regarding the prohibition of many other poor life style habits.

The fact is that there are many other bad life style habits leading to worse health outcomes such as (childhood) obesity [2]. In this case we must also prohibit the sale of for example Big Mac Meals to children. You might imagine that it is too difficult to draw a line between unhealthy and that what is unhealthy to such a degree that prohibition is justified.

An alternative and more realistic manner to deal with this increasing health problem might be able to establish by the education of children at an early age regarding the dangers of energy drinks and other poor eating and drinking habits. The Government should have a more active role in promoting and sponsoring activities in order to educate and stimulate children for a better life style. Teachers also have an important role in warning their students against the negative effects of energy drinks and other poor eating habits. However, parents still have the primary responsibility, therefore they should also be informed.

A ban on the sale of energy drinks to youngsters sounds logical, but might be a challenging solution in real-world practice. The most important step forward to deal with this problem is to educate and provide good information about energy drinks and other poor life style habits to youngsters.

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References

1. *Seifert, S.M., et al., An analysis of energy-drink toxicity in the National Poison Data System. Clin Toxicol (Phila), 2013. 51(7): p. 566-74.*
2. *Pulgaron, E.R. and A.M. Delamater, Obesity and type 2 diabetes in children: epidemiology and treatment. Curr Diab Rep, 2014. 14(8): p. 508.*

The dissection of Williams syndrome: searching for the gene coding for positive emotionality

Williams syndrome is a rare neurodevelopmental disorder characterized by: a distinctive facial appearance, along with a low nasal bridge; an unusually cheerful demeanor and ease with strangers; developmental delay coupled with strong language skills; and cardiovascular problems, such as supravalvular aortic stenosis and transient hypercalcemia.

It is caused by a deletion of about 26 genes from the long arm of chromosome 71. The syndrome has an estimated prevalence of 1 in 10,000 births2. Williams syndrome is caused by the spontaneous deletion of genetic material from the region q11.23 of chromosome 7. The deleted region includes more than 25 genes, and the loss of several of these genes probably contributes to the characteristic features of this disorder. CLIP2, ELN, GTF2I, GTF2IRD1, and LIMK1 are among the genes that are typically deleted in people with Williams syndrome. Researchers have found that loss of the ELN gene, which codes for the protein elastin, is associated with the connective-tissue abnormalities and cardiovascular disease (specifically supravalvular aortic stenosis and supravalvular pulmonary stenosis) found in many people with this syndrome.

Despite their physical and cognitive deficits, individuals with Williams syndrome exhibit impressive social and verbal abilities. Williams patients can be highly verbal relative to their IQ. Some other strengths that have been associated with Williams syndrome are auditory short-term memory and facial recognition skills. The language used by individuals with Williams syndrome differs notably from unaffected populations, including individuals matched for IQ. One of deleted genes, GTF2I, has been associated with hypersociability3.
In this issue of the journal Chin-See-Chong et al describe a candidate gene study, in which they assessed a possible correlation between two polymorphisms of the GTF2I gene and positive emotionality in 3-year old children (n=862) , using data from the Generation R study4.

Positive emotionality was measured by two observational tests (the Puppet Game and the Popping Bubbles). The authors found a trend to positive emotionality and one of the SNPs of the GTF2I gene. However, as the authors state, more research is warranted to draw conclusions about the possible genetic contribution to positive emotionality. They suggest that studying expression levels of GFT2I between cases and controls may be a promising approach.

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References

1. *Martens MA, Wilson SJ, Reutens DC. Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. J Child Psychol Psychiatry 2008; 49: 576-608.*
2. *Lenhoff HM, Teele RL, Clarkson PM, Berdon WE. John C. P. Williams of Williams-Beuren syndrome. Pediatric Radiology 2010; 41: 267–269.*
3. *Jarvinen A, Korenberg JR, Bellugi U. The social phenptype of Williams syndrome. Curr Opin Neurobiol 2013; 23: 414-422.*
4. *Jaddoe VW, van Duijn CM, Franco OH. The Generation R study: design and cohort update 2012. Eur J Epidemiol 2012; 27: 739-756.*

Systematic Review

The long-term effects of maternal obesity during pregnancy on the health of the offspring

A systematic review

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Abstract

Objective: **To evaluate whether there is an effect of maternal obesity during pregnancy on the long-term health of the child.**
Methods: **The database PubMed was searched in January 2014 to identify relevant studies in English. Studies that focused on maternal obesity and the impact on the health of the offspring were included.**
Results: **Six studies were included in this review. Two studies reported a higher risk of developing asthma, one a higher risk of developing metabolic syndrome and one a higher risk of developing attention deficit hyperactivity disorder (ADHD). The two remaining studies found higher inflammation markers and a higher risk of all-cause mortality and hospital admission after a cardiovascular event.**
Conclusions: **These data show that offspring have a greater risk in developing asthma, metabolic syndrome, ADHD and higher levels of hs-CRP later in life. Also, the all-cause mortality is higher in the offspring when the mother was obese during pregnancy. Maternal obesity therefore does appear to have an effect on the health of the offspring. Hence, it is of great importance to prevent exposure of offspring to preconceptional maternal obesity and from the early embryonic period onwards. For this reason, lifestyle modification is of great importance for obese women with a wish to conceive.**

Introduction

Obesity is one of the fastest growing health problems in the western world. The prevalence of this problem among pregnant women is also increasing. In this review, obesity is defined as a body mass index (BMI) ≥30kg/m2. In the United Kingdom the prevalence of obese women at reproductive age doubled in the period 1993-2008. A total number of 47,500 women per year required high dependency care in England because of obesity. [1]

It is well known that obesity is associated with several chronic diseases such as type-2-diabetes and impairment of immune function.[2] New connections are still being discovered. Additionally, obesity is a significant risk factor for short-term maternal complications during pregnancy. The Confidential Enquiry into Maternal and Child Health report showed that between 2003 and 2005, 28% of maternal deaths where obese, whereas the prevalence of obesity was 16-19% in the general maternity population.[3] Not only are miscarriages more likely when obese, but later in gestation there is also an increased risk of pre-eclampsia, gestational hypertension and gestational diabetes.[4] In case of obesity there is also an increased risk for fetal complications such as the development of fetal macrosomia and congenital abnormalities.

The Barker hypothesis also known as fetal programming, suggests that nutrition and other influences for the mother during gestation set the body organs and systems of the offspring for life.[5] The growth and development of the embryo are very important for the health of the baby later in life. The mother needs to create the best intra-uterine environment as possible for the child, before and during the pregnancy. Harmful exposures before and during the beginning of the pregnancy contribute to the susceptability for complications during pregnancy and diseases later in life.[6]

A review by Painter et al., based on a cohort study which included 2,414 people aged 50 and born around the time of the 1944-1945 famine in the Netherlands, reported an association between exposure to famine in gestation and, inter alia, coronary heart diseases, obstructive airways diseases and decreased glucose tolerance.[7] These findings show the impact of malnutrition before and during gestation. A small size at birth, because of undernutrition in utero, is associated with coronary heart disease.[8] Furthermore being born in the Chinese famine areas is associated with a high risk of metabolic syndrome later in life.[9] These reviews however only focused on undernutrition.

With the growing prevalence of obesity, it is useful to investigate whether a similar effect is found in overnutrition. It is necessary to have a list of the complications of maternal obesity and to learn how to prevent them. The objective of this review is to evaluate the findings on the effect of obesity during pregnancy on the long-term health of the child.

Methods

Search strategy

The PubMed database was searched for English-language articles published between the beginning of the database and January 2014, using the following search term: Obesity [Majr] AND pregnancy [Mesh] AND body mass index [Mesh] AND "maternal" AND "offspring".

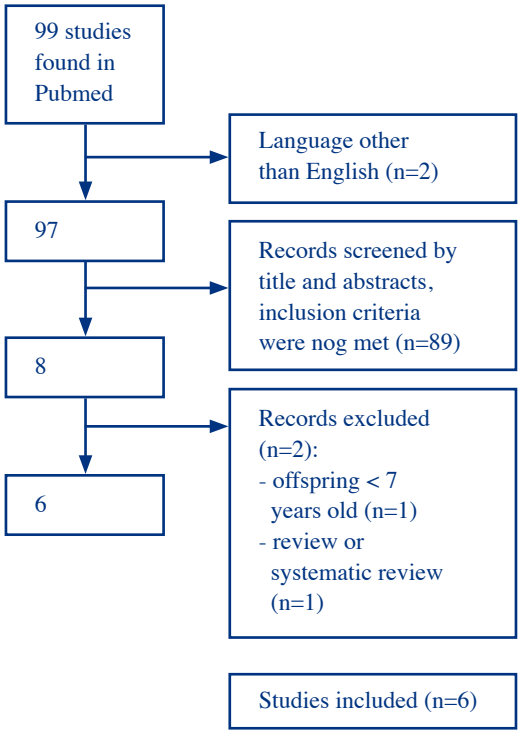
Study selection

Two researchers screened each study by title and abstract. Only studies that focused on maternal obesity and the impact on the health of the offspring were included. Exclusion criteria were: offspring younger than seven years of age, review articles, research focused on gestational weight gain. Cases are defined as offspring of mother with a BMI ≥30kg/m2. Controls are defined as offspring of mother with a BMI <30kg/m2. These definitions were also used in almost all the studies.

Results

Our PubMed search produced 99 publications. A total number of 93 studies that did not meet the inclusion criteria were excluded. Studies in languages other than English were also excluded (Fig.1).

Figure 1- Flowchart of the selected studies



Description of studies

Descriptive data for studies included in the review are listed in alphabetical order (Table 1). The six studies included are quite heterogeneous. Five studies are cohort studies and one study is a cross-sectional study, but based on a cohort. The studies were conducted in Europe (n=4) and the United States (n=2). Five studies included cases that were still children (aged between 6-16). Only one study contained mature cases (aged between 34-61). Most of the maternal BMI data was gathered through measurement by a study controller (n=3) and the other data was gathered by self-report (n=2). Every study evaluated the effect of maternal obesity on the health of the offspring, however they all focused on different outcomes. Two studies focused on the presence of asthma symptoms; one study on metabolic syndrome (MS); another evaluated the risk of attention deficit hyperactivity disorder (ADHD) in the offspring; another study on outcome parameters cytokines and inflammatory markers and lastly, one study focused on 'all-cause mortality' and hospital admission caused by a cardiovascular event.[10-15]
The definition of MS is fulfilled by 3 of 5 major criteria: obesity determined by waist circumference; hypertension; low HDL levels; elevated triglyceride levels and glucose tolerance. 'All-cause mortality' is defined as deaths from any unspecified cause.

The effect of maternal obesity

The studies reviewed all focused on different outcomes (Table 2).

Two studies, both partially focused on asthma symptoms can be evaluated together. The first study, a cohort study from Finland, reported a significant higher risk of developing asthma symptoms, with OR=3.51 (95% CI: 1.60-7.68) for 'ever wheeze' and with OR=4.03 (95% CI: 1.54-10.54) for 'current wheeze'. The other study, a cohort study from Denmark, also reported a significant association between maternal obesity and asthma symptoms. This study distinguishes two groups: women with a BMI between 30 and 35 (Group 1) and women with a BMI greater than 35 (Group 2). The authors of the study also named three types of wheezing: early transient wheezing (ETW), persistent wheezing (PW) and late-onset wheezing (LOW). For Group 1 there was a higher risk of developing all sorts of wheezing: ETW with OR=1.29 (95% CI: 1.16-1.44), PW with OR=1.62 (95% CI: 1.26-2.09) and LOW with OR=1.48 (95% CI: 1.16-1.89). The study also reported a higher risk for Group 2: ETW with OR=1.33 (95% CI: 1.10-1.60) and LOW with OR=1.87 (95% CI: 1.28-2.73).

One cohort study from Philadelphia, USA, makes a connection between the risk of MS and maternal obesity. The study describes a two-fold increased risk of MS with HR=1.81 (95% CI: 1.03-3.19). However, this only applies with a maternal BMI greater than 27.3.

One study reported the association between maternal obesity and the risk of developing ADHD in the offspring. In this cohort study, an association between maternal weight in pregnancy and high ADHD symptoms has been found. Maternal obesity led to greater risk of high ADHD symptoms with OR=1.89 (95% CI: 1.13-3.15).

Table 1 - Descriptive data for studies focused on maternal obesity and the effect on the health of the offspring

Study	Study design	Case/control	Age range (years)	Source of maternal BMI data	Case identification	Outcome
Boney et al., 2005	Longitudinal cohort study	93/179	6-11	Measured	Measurements	Metabolic syndrome
Harpsøe et al., 2013	Cohort study	2,689/36,185	7	Self-reported from interview	Self-reported from interview	Asthma, wheezing, atopic eczema and hay fever
Leibowitz et al., 2012	Cross-sectional study	16/34	12	Self-report	Tanner stage self-assessment forms	Cytokines and inflammatory markers
Patel et al., 2012	Prospective cohort study	6945	15-16	Measuring and a questionnaire	Self-report data from the ISAAC questionnaire	Ever wheeze or current wheeze
Reynolds et al., 2013	Record linkage cohort study	1,550/27,051	34-61	Measured	Database	All-cause mortality and hospital admission with a cardiovascular event in adult offspring.
Rodriguez et al., 2008	Follow-up of prospective pregnancy cohorts	223/12,753	7-12	Data recorded in the medical chart	Rated by teachers by the SDQ and the RB2	High ADHD symptom score

The cross-sectional study from Rhode Island, USA, focused on inflammation in 12-year-old children due to maternal obesity. This study did not report a significant difference in inflammatory markers between the cases and the control data. The authors did however report higher hs-CRP levels in children of women who were obese during pregnancy (OR=16.23 (95% CI: 2.14-123.12)).

Finally, one cohort study, conducted in England, reported a link between all-cause mortality in adult offspring and maternal obesity with HR=1.35 (95% CI: 1.17-1.55). According to this study it is more likely to die before the age of 55 with HR=1.42 (95% CI: 1.19-1.69). The study further shows an association between hospital admission with a cardiovascular event in the adult offspring and obesity of the mother during pregnancy. When the mother is obese while pregnant, there is more risk of being hospitalized due to a cardiovascular event in the offspring with OR=1.29 (95% CI: 1.06-1.57).

Discussion

Maternal obesity has different effects on the long-term health of the child. Offspring have a greater risk of developing asthma symptoms, MS and higher levels of hs-CRP. The all-cause mortality is higher in the offspring. Furthermore the evidence suggests offspring of women obese during pregnancy develop higher ADHD symptom scores. It is shown that maternal obesity is a great risk factor for several diseases in the offspring and it is therefore important to prevent obesity in women who plan to become mothers.

Research for the long-term health of offspring from obese mothers is relatively new. It was therefore difficult to find relevant and available information. The studies that did research this field all focused on different outcomes parameters. In this sense it was difficult to combine all the information obtained.

The articles included in the study have their strengths and limitations. Harpsøe et al., used 38,874 mother-child pairs in their cohort study. The researchers distinguished overweight and obesity. It is relevant to know if there is any difference between these groups so as to differentiate between the effect of the extent of obesity.

Furthermore the authors searched for confounders and made adjustments (Table 2). A big limitation of the study was the method of collecting data (telephone interviews and questionnaires). Self-reporting can lead to misclassification of the results. Hence, this might affect the results.

Patel et al., also had a large cohort (6,945 adolescents), which gives a good image of the population mean. Another strength of their study are the adjustments they made (Table 2). The use of self-reporting however is an important drawback of collecting of data.

Boney et al., examined the development of MS among large-for-gestational-age (LGA) and appropriate-for-gestational-age (AGA) children. They also differentiated between mothers with gestational diabetes mellitus (GDM) and without GDM. It is important to consider differences between groups to obtain relevant information and classify correctly. A limitation of this study was the aberrant definition of maternal obesity. The authors define a BMI of >27.3 as obese. Finally, it is not clear if the study searched for confounders or if it made any adjustments.

In the study by Rodriquez et al., self-reporting and medical records were used for evaluation of for pre-pregnancy BMI. Furthermore they used a large cohort of 12,556 school-aged children. They also searched for confounders and made adjustments (Table 2).

However, rating of the outcome parameters (inattention and hyperactivity symptoms) was done by the teachers of the children (instead of professionals). Additionally, rating was done by using different scales. Moreover, it is important to mention also that a high ADHD symptom score does not equate to a ADHD diagnosis. In this study a distinction was made between different weight groups. However, the definition of these groups was not stated.

Obesity is known to be a chronic inflammatory state, but it is unclear if maternal obesity influences the development of inflammation in the offspring. hs-CRP may be an early risk factor for excess weight gain in children exposed to obesity during pregnancy.

Table 2 - The effects of maternal obesity on offspring

Study	Effect of maternal obesity on offspring	Other findings	Adjustments
Boney et al., 2005	Increased risk on MS HR: 1.81 (1.03-3.19)*		
Harpsøe et al., 2013	DD asthma ever[3]: 30 ≤ BMI < 35 adjusted OR: 1.54 (1.34–1.76), ≥ 35 adjusted OR: 1.52 (1.21-1.91)		Sex of the child, maternal age at conception, maternal smoking during first trimester, number of older siblings, maternal history of allergy, and mutually adjusted for pre-pregnancy BMI and gestational weight gain.
	PDD asthma[3]: 30 ≤ BMI < 35 adjusted OR: 1.50 (1.24-1.81), ≥ 35 adjusted OR: 1.55 (1.14-2.11)		
	CDD asthma[3]: 30 ≤ BMI < 35 adjusted OR: 1.58 (1.32-1.90), ≥ 35 adjusted OR: 1.48 (1.08-2.04)		
	ETW: 30 ≤ BMI < 35 adjusted OR: 1.29 (1.16-1.44), ≥ 35 adjusted OR: 1.33 (1.10-1.60)		
	PW: 30 ≤ BMI < 35 adjusted OR: 1.62 (1.26-2.09)		
	LOW: 30 ≤ BMI < 35 adjusted OR: 1.48 (1.16-1.89), ≥ 35 adjusted OR: 1.87 (1.28-2.73)		
Leibowitz et al., 2012	Hs-CRP in mg/L, detectable versus undetectable adjusted OR: 16.23 (2.14-123.12)**	High risk children (of obese mothers) have a higher BMI than low risk children (mean±SD: low risk 17.9±2.5, high risk 22.3±6.8,*)	BMI z-score, gender, Tanner stages
Patel et al., 2012	Ever wheeze: no parental atopy adjusted OR: 3.51 (1.60-7.68) **		Social class at birth, marital status at birth, maternal education, maternal asthma, birth weight, parental smoking during gestation, and adolescent BMI at age 15 years.
	Current wheeze: no parental atopy adjusted OR: 4.03 (1.45-10.54)**		
Reynolds et al., 2013	All-cause mortality adjusted HR: 1.35 (1.17-1.55)	All-cause mortality before age 55 adjusted HR: 1.42 (1.19-1.69)	Gestation when weight was measured, maternal age at delivery, social class, current age of offspring, birth weight, sex of offspring.
	More hospital admissions adjusted HR: 1.29 (1.06-1.57)		
Rodriguez et al., 2008	High ADHD symptom score fully adjusted model OR: 1.89 (1.13-3.15)		Smoking during pregnancy, maternal education, maternal age, gestational age, birth weight, infant sex, family structure

[1] BMI > 27.3
[2] HR or OR with 95% CI. *P-value < 0.05. **P-value <0.01
[3] Docter-diagnosed = DD. Previous docter-diagnosed = PDD. Current docter-diagnosed = CDD.

Adjustments were made, by Leibowitz et al., for some confounding factors (i.e. BMI z-score, gender and Tanner stages). This is a strength but there are more confounders which need to be adjusted. In this study self-reporting was used for collection of data and they are based on a small sample size (50 subjects). Furthermore the effect of high inflammatory markers on clinical parameters was not evaluated.

The study of Reynolds et al., used a big cohort with 37,709 people. A distinction was made between overweight and obese mothers. Furthermore, height and weight of the mothers were measured at the first antenatal visit. Additional strengths are the adjustments they made (Table 2). The study only reported hospital admissions for offspring. As a consequence offspring without any hospital admissions, i.e. healthy offspring, remained unlinked to the database. This is considered a limitation of the study. Finally, the admission of the offspring is causally related to the direct effect of maternal obesity on the developing child instead of taking account of other effects (i.e. shared genetic factors and postnatal lifestyle factors) on the development of obesity and cardiovascular risk factors later in life.

A concern to be aware of is the correlation between maternal (gestational) diabetes and obesity. Both have their risks for the offspring. Intrauterine exposure to diabetes is associated with an excess of diabetes and obesity in the offspring.[16]

There is however a greater risk in developing maternal (gestational) diabetes when the mother is obese. It cannot be determined if the consequences for the offspring are caused by the obesity or by the diabetes. Oostvogels et al., show that high maternal pre-pregnancy BMI and postnatal accelerated growth are associated with adverse metabolic components in early childhood.[17] It appears that a high pre-pregnancy BMI has an effect on the metabolic processes in the preconception period. It cannot be determined whether the cause of disease for the offspring is related to diabetes or to obesity. It is known that obesity can be seen as an effect of the preconception period and maternal (gestational) diabetes as an effect of the pregnancy.

There are some studies that researched the possible underlying mechanisms of the health conditions in offspring of obese mothers. Rabadán-Diehl and Nathanielsz demonstrated that altered DNA methylation patterns of genes are associated with cardiovascular disease, metabolism and inflammation. This was established in individuals that were exposed to famines in utero and similar histone and DNA changes in several tissues in animal models such as adipose tissues, pancreas and placenta.[18]

The review article of Rhee et al., confirmed that the FTO gene has an association with increased weight at 2 weeks of age. Those who are homozygous for the at-risk allele have been found to be 3kg heavier than those who do not have the allele. Another important gene is the MC4R gene. When α-MSH binds to MC4R, individuals begin to feel satiated and increase energy expenditure through thermogenesis. Mutations in the gene can lead to rare familial forms of severe obesity. It is increasing consumption and decreasing expenditure of energy.[19] More research is required to establish if there are more genes or more causes for the association between maternal obesity and the effects for the offspring.

It is important to know the long-term effects of maternal obesity. The described effects have serious consequences for the health of the offspring. The authors conclude that people should be aware of these effects, with obesity as one of the fastest growing health problems. Knowing the impact of maternal obesity on the health of the offspring can be used to convince women at reproductive age to lose weight. This study shows the importance of early prevention of obesity in children by developing a healthy lifestyle so as to prevent maternal obesity in the future.

It is recommended to continue research of the long-term health of offspring whose mothers were obese before or during pregnancy. Thus far few effects are known, but the effects found indicate life-threatening consequences. To create a healthy life for future generations, the authors stress the importance of gaining better insight into the effects of overnutrition during early life.

References

1. *Heslehurst N, Rankin J, Wilkinson JR, et. al. A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989-2007. Int J Obes (Lond). 2010; 34: 420-8*
2. *Sanz Y, Moya-Pérez A. Microbiota inflammation and obesity. Adv Exp Med Biol. 2014; 817: 291-317*
3. *Modder J, Fitzsimons KJ. Management of women with obesity in pregnancy. CMACE/RCOG joint guideline. 2010: 2*
4. *Catalano PM, Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. BJOG 2006; 113: 1126-33.*
5. *Barker DJ. Maternal nutrition, fetal nutrition, and disease in later life. Nutrition. 1997; 13: 807-13.*
6. *Steegers EAP. Embryonale gezondheid en preconceptiezorg: belang voor huidige en toekomstige generaties. Ned Tijdschrift Geneeskd. 2014; 158: A7373*
7. *Painter RC, Roseboom TJ, Bleker OP. Prenatal exposure to the Dutch famine and disease in later life: an overview. Reprod Toxicol. 2005; 20: 345-52.*
8. *Stein CE, Fall CH, Kumaran K, et al. Fetal growth and coronary heart disease in south India. Lancet. 1996; 348: 1269-1273)*
9. *Li Y, Jaddoe VW, Qi L, et al. Exposure to the chinese famine in early life and the risk of metabolic syndrome in adulthood. Diabetes care. 2011; 34: 1014-1018*
10. *Harpsoe MC, Basit S, Bager P, et al. Maternal obesity, gestational weight gain, and risk of asthma and atopic disease in offspring: a study within the Danish National Birth Cohort. J Allergy Clin Immunol. 2013; 131: 1033-40.*
11. *Patel SP, Rodriguez A, Little MP, et al. Associations between pre-pregnancy obesity and asthma symptoms in adolescents. J Epidemiol Community Health. 2012; 66: 809-14.*
12. *Boney CM, Verma A, Tucker R, et al. Metabolic Syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005; 115: e290-6.*
13. *Rodriguez A, Miettunen J, Henriksen TB, et al. Maternal adiposity prior to pregnancy is associated with ADHD symptoms in offspring: evidence from three prospective pregnancy cohorts. Int J Obes (Lond). 2008; 32: 550-7.*
14. *Leibowitz KL, Moore RH, Ahima RS, et al. Maternal obesity associated with inflammation in their children. World J Pediatr. 2012; 8: 76-9.*
15. *Reynolds RM, Allan KM, Raja EA, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. BMJ 2013;347: f4539.*
16. *Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes. 2000; 49: 2208-11*
17. *Oostvogels AJ, Stronks K, Roseboom TJ, et al. Maternal pre-pregnancy BMI, offspring's early postnatal growth and metabolic profile at age 5-6 years: the ABCD-study. J Clin Endocrinol Metab. 2014; jc20141561*
18. *Rabadán-Diehl C, Nathanielsz P. From Mice to Men: research models of developmental programming. J Dev Orig Health Dis. 2013; 4: 3-9*
19. *Rhee KE, Phelan S, McCaffery J. Early determinants of obesity: genetic, epigenetic, and in utero influences. Int J Pediatr. 2012; 2012:463850*

Can adrenaline safely be used in local anaesthesia involving distal extremities?

A systematic review

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Summary

Objective: **Addition of adrenaline in local anaesthesia of distal extremities with lidocaine remains a subject of debate. Surgery textbooks recommend not to use adrenaline, because its use could result in vasoconstriction and ischemic injury. However, these conclusions are based on dated articles. We performed a systematic review on the available literature to investigate the safety of the use of adrenalin in local anaesthesia of distal extremities.**

Methods**: We searched the Pubmed database for articles published in English addressing the use of adrenaline in anaesthesia of distal extremities (digital block anaesthesia) using lidocaine.**

Results**: Using our search strategy, we found 11 relevant articles, including 4 reviews, 4 randomised controlled trials, 1 retrospective and 2 prospective cohort studies, together involving more than 4400 patients. There were no reported vascular or ischemic incidents involving the use of adrenaline supplemented lidocaine. The use of adrenaline reduced the total amount of lidocaine used, and resulted in a reduced number of bleeding incidents.**

Conclusion**: Adrenaline can be safely applied in local anaesthesia of distal extremities with lidocaine, and does not result in ischemic injury when a normal functioning vasculature is present. The ancient textbook dogma not to use adrenaline should be revisited.**

Introduction

Local anaesthesia is routinely used for surgical procedures. In 1884, Koller for the first time used cocaine to obtain local anaesthesia of the cornea.[1] 5 years later, Strauss used cocaine in a digital block while treating an ingrown toenail.[2-4] Procaine was subsequently developed in 1904 by Einhorn. Because of the vasodilatory effect of this anaesthetic, Braun proposed the addition of adrenaline (epinephrine), to obtain vasoconstriction, resulting in a better hemostatic effect. Adrenaline induces this hemostatic effect, by binding to the alpha-1 and alpha-2 receptors. This causes a vasoconstrictive effect, by activating the phosphatidylinositol system and adenylate cyclase pathways. In these early days, adrenaline was added manually to the anaesthetic prior to use, resulting in a wide variation of adrenaline dilutions used. The nowadays most frequently used amide anaesthetic lidocaine (xylocaine), was first produced in 1943 by Lofgren and Lundquist. Lidocaine had the advantage of a reduced allergenicity, a faster onset, higher efficiency and a longer duration of anaesthesia compared to the previously used ester-containing medications.[2-3]

Lidocaine is these days most often used in combination with adrenaline, at standardized concentrations varying between 1:80 000-1:100 000 (10-12.5 µg/ml). General surgical textbooks traditionally do not recommend the use of adrenaline when local anaesthesia is required for distal extremities, including fingers, toes and ears, because adrenaline could possibly cause vasoconstriction of distal end arteries, resulting in ischemic injury due to reduced or absent blood flow.[5-7] Although this recommendation is generally found in many surgical textbooks, and instructions to medical students (for example provided at Skills plaza of the Erasmus MC) the scientific evidence supporting this recommendation is often less obvious. We here asked the question whether the use of adrenaline in anaesthesia of the distal extremities using lidocaine harbours increased risk of ischemic injury.

Table 1 - Overview of the primary research papers obtained in our Pubmed search.

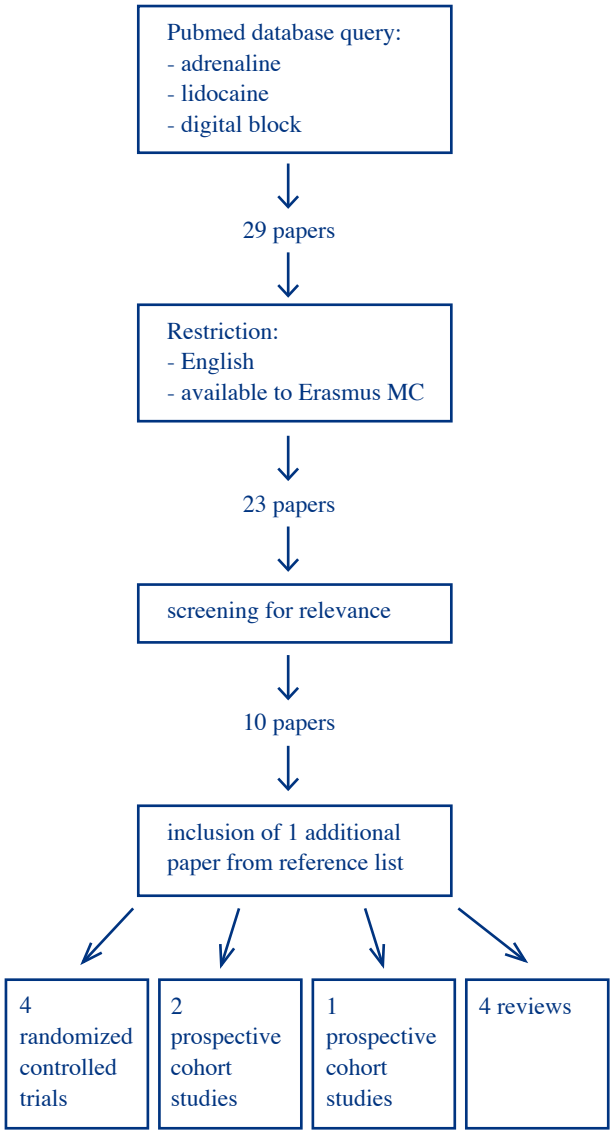
Reference	Type of Study	Patients & Groups	Type of surgery	Outcome	Conclusions	Comment
Wilhelmi et al 2001 [8]	RCT	Group A (n=29) lidocaine 1% Group B (n=31) Lidocaine 1% + adrenaline 1:100 000	Digital block of fingers for traumatic injury or elective procedures	Reduced number of re-injections (p=0.098), bleedings (p=0.002) and complications (p=0.23) in adrenaline group	Use of adrenaline is safe, and reduces the number of re-injections, bleedings and complications	
Andrades et al 2003 [9]	RCT	Group A (n=22) lidocaine 2% Group B (n=21) lidocaine 2% + adrenaline 1:100 000	Digital block of fingers for traumatic injury or elective procedures	Time after injection till start of surgery shorter and less reinforcements (p<0.05), risk of bleeding and systemic complications (p<0.05) lower in adrenaline group. Duration of anaesthesia shorter in lidocaine only group. No ischemic complications in both groups	Use of adrenaline is safe, prolongs the duration of anaesthesia and reduces the risk of bleedings and systemic complications	
Sönmez et al 2008 [10]	RCT	Group A (n=10) lidocaine 2% Group B (n=10) Lidocaine 2% + adrenaline 1:80 000	Digital block of fingers for elective procedures	Capillary peripheral blood parameters prior to and 15 min after block were not significantly different between both groups. Anaesthesia was prolonged in adrenaline group (p=0.001).	Adrenaline use is safe when normal vasculature is present	Small study. Patients suffering from vascular disease were excluded.
Altinyazar et al 2010 [11]	RCT	Group A (n=22) lidocaine 2% Group B (n=22) lidocaine 2% + adrenaline 1:100 000	Digital block for ingrown toenails	Mean anaesthetic volume smaller and duration of drainage shorter in adrenaline group (p<0.001). Postoperative pain similar in both groups	Adrenaline is safe, and results in less anaesthetic used, and diminish the drainage time	
Chowdhry et al 2010 [12]	Retrospective cohort	Group A (n=500) lidocaine 1% Group B (n=611) lidocaine 1% + adrenaline 1:100 000	Digital block of fingers and hands for traumatic injury or elective procedures	No gangrene, delayed wound healing or nerve damage in any patient (n=968 followed up).	The use of adrenaline is safe in terms of ischemic complications, and reduces the total amount of anaesthetic used	Patients suffering from vascular disease were only included in the lidocaine-only group. Unclear how outcome values are determined. High level of drop-out from follow-up (unclear whether equal between groups)
Lalonde et al 2005 [18]	Prospective cohort	Group A (n=3110) lidocaine 1% + adrenaline 1:100 000	Digital block of fingers and hands for traumatic injury or elective procedures	No cases of ischemic injury. Phentolamine rescue was not required	Use of adrenaline is safe in digital block anaesthesia	Largest reported group of patients. Patients suffering from vascular disease were excluded
Altinyazar et al 2004 [13]	Prospective cohort	Group A (n=24) lidocaine 2% + adrenaline 1:100 000	Digital block of fingers and toes for traumatic injury or elective procedures	Color Doppler flow imaging shows normalized blood flow between 60 to 90 min after start of digital block. No systemic complications observed	Use of adrenaline is safe in digital block anaesthesia in selected patients	Patients suffering from vascular disease were excluded

Legend: RCT, randomised controlled trials. N, number of patients included in the indicated groups.
If available, p-value is indicated to show significance obtained after statistical testing.

Methods

On July 18th, 2014 we searched the Pubmed database for papers useful for our review. We used the search terms "adrenaline", "lidocaine" and "digital block" ("epinephrine"[MeSH Terms] OR "epinephrine"[All Fields] OR "adrenaline"[All Fields]) AND ("lidocaine"[MeSH Terms] OR "lidocaine"[All Fields]) AND digital[All Fields] AND block[All Fields], and included only articles published in English and available to the medical library of the Erasmus MC. The obtained papers were screened by the information provided in the abstract, and relevant papers were included in the analysis. To be included in our study, papers should study the use of adrenaline in anaesthesia of the distal extremities, and should have an evaluation of the safeness of using adrenaline as the main research question. Papers not dealing with our central question were excluded. In addition, we included relevant papers included in the reference list of the primary papers; when required, the corresponding author of the papers was contacted to obtain a digital version of a paper which was not available to the Erasmus MC medical library.

Figure 1- Flowchart showing our literature search



Results

Using our search strategy, we found 29 papers, of which 28 were published in English, and 23 were available to the Erasmus MC (Figure 1). After screening of the abstracts, we found 10 papers which were relevant for our subject, including 4 randomised controlled trials[8-11], 1 retrospective [12] and 1 prospective cohort[13] studies and 4 reviews.[14-17] In addition, we included one additional prospective cohort study[18] which was found in the reference list of several primary papers, but which was not detected using our search strategy. Table 1 summarizes the 7 primary research papers which are discussed in this review. In addition to these 7 papers, we will discuss the outcome of one of the reviews below.

Denkler addressed in his historical review published in 2001 all published cases of complications during local distal block anaesthesia using adrenaline.[14] In his extensive literature review, covering papers published between 1880 and 2000, he only found 48 cases reporting digital gangrene after local anaesthesia using cocaine or procaine. Only 21 of these cases involved the use of adrenaline. In 17 of these cases, manually diluted adrenaline of unknown concentration was used. In addition, the majority of these cases reported confounding factors, such as the use of hot soaks, infection and tight tourniquets, which will likely have contributed to the development of gangrene in these cases. Hence it is unclear to what extend the use of adrenaline has contributed. Peculiar, after the introduction of lidocaine with standardized concentrations of adrenaline in 1948, no further cases of digital gangrene have been reported. Only the use of Epipen auto-injectors to treat anaphylaxis has since been reported to cause digital gangrene;[19-21] however, in these cases much higher concentrations of adrenaline (1:1000) were used compared to concentrations used in local anaesthesia (most often 1:100 000).

Wilhelmi et al performed a double-blinded randomized controlled trial involving 60 patients undergoing surgical procedures of the fingers for either traumatic injury or elective procedures.[8] Group A consisted of 29 patients undergoing digital block (Oberst) anaesthesia using lidocaine 1%. In group B, 31 patients were included which were injected with lidocaine 1% supplemented with adrenaline 1:100 000. In the adrenaline group, a single patient required an additional injection before surgery could be finalized, whereas 5 patients in the lidocaine-only group required re-injection (p=0.098). The number of bleedings requiring additional interventions was lower in the group B (n=9), compared to group A (n=20, p=0.002). Also the number of complications after surgery was lower in the adrenaline compared to the lidocaine-only group (n=0 vs n=2, p=0.23). The authors concluded that adrenaline can safely be used in anaesthesia of distal extremities, is likely to reduce the number of bleedings, and can prolong the duration of anaesthesia. Similar conclusions were derived in another double-blinded randomised controlled trial involving 43 patients in an emergency department in Chile.[9] Andrades et al injected 22 patients with lidocaine 2%, and 21 patients with lidocaine 2% and adrenaline 1:100 000. In both groups, patient characteristics, such as age, sex and indication for surgery (post-traumatic and elective) were comparable.

After injection, surgery could be started in a significantly shorter time frame and required less reinforcements in the group injected with adrenaline ($p<0.05$). The risk of bleeding and systemic complications were also lower in this group. The duration of anaesthesia was shorter in the lidocaine-only (2.4 hours) compared to the adrenaline group (4.6 hours, $p<0.05$), and no incidents involving ischemic complications were reported in that study.

Chowdhry et al retrospectively analysed 1111 cases of patients undergoing 4 finger or hand surgery for a broad range of indications, performed by a single surgeon during 7 years in an American clinic.[12] 500 patients underwent anaesthesia using lidocaine 1% (2-10 ml, on average 5.7 ml), and 611 patients were injected with lidocaine 1% supplemented with adrenaline 1:100 000 (0.5-10 ml, on average 4.3 ml). 968 patients were followed-up for a non-specified period (88.75%), and none of the patients developed gangrene, delayed wound healing or nerve damage. Of note, patients suffering from pre-existent vascular diseases, or were vascular compromised due to injury were excluded from the adrenaline group. The largest prospective cohort study was performed by Lalonde and colleagues in Canada, involving 3110 consecutive cases involving injection with lidocaine and adrenaline 1:100 000.[18] 1340 injections involved fingers (involving procedures for trigger fingers, lacerations, tendon surgery amongst others), and 1770 injections were placed in hands (involving surgery for carpal tunnel and de Quervain's release, excisions for wrist ganglions amongst other procedures), involving patients varying in age from 1 day till 93 years. In none of the cases, ischemic injury occurred. Phentolamine rescue, a method to counteract adrenaline-based vasoconstriction, [22-25] was not required. Also these authors conclude that adrenaline can safely be used when performing anaesthesia of distal extremities.

Sönmez and colleagues investigated whether the use of adrenaline resulted in a measurable change of capillary blood parameters.[10] They injected 20 patients with 3 ml anaesthetic randomizing between lidocaine 2% and lidocaine 2% with adrenaline 1:80 000, and measured capillary blood parameters prior to the block and after 15 minutes. Patients suffering from peripheral vascular disease, diabetes mellitus, Reynaud's or CREST syndrome or systemic sclerosis were excluded. The pCO2, pO2, SaO2 or HCO3 did not significantly change in the adrenaline group after pacing the block. In addition, also these authors found that anaesthesia was longer maintained in the adrenaline group compared to the lidocaine-only group (8.1 vs 4.8 hours). In another study investigating blood flow by color Doppler flow imaging in distal arteries after injection with lidocaine 2% with adrenaline 1:100 000 involving 24 patients (again patients suffering from vascular disease were excluded) it was found that blood flow was normalized after 60 to 90 minutes after the start of the procedure.[13] Patients underwent a 10 day follow-up, in which also no complications were observed. The same authors performed a randomised trial in 44 patients undergoing digital block (lidocaine 2%) with and without adrenaline (1:100 000) during chemical matricectomy with phenol for ingrown toenails.[11] Also during this procedure, the use of adrenaline was safe, and resulted in a lower anaesthetic volume used, and a shorter postoperative drainage period.

Discussion

We found in our systematic review of the available literature that adrenaline at a concentration ranging from 1:80 000-1:100 000 can safely be used in local anaesthesia of distal extremities using lidocaine. Our findings contradict the common textbook recommendations not to use adrenaline in surgery involving distal 5 extremities, and can have important implications for patient care in Emergency Departments and General Practitioner clinics. In medical practise, most often even lower concentrations of adrenaline (1:200 000) are used in standard prepared anaesthetics, compared to the concentrations used in the studies reviewed in this paper which were found to be in safe range. The classical dogma not to use adrenaline seems to be based on a limited number of cases using cocaine and procaine as anaesthetic, published before 1950,[14] and it is an interesting phenomenon why this dogma has been maintained for such a long time despite the available contradicting evidence. Although the available randomised controlled trials comparing lidocaine with lidocaine supplemented with adrenaline are performed in small groups of patients,[8-9] their outcome is similar and consistent. Also in the cohort studies investigating more than 3000 patients,[12,18] no complications were found in patients who used adrenaline. Studies investigating the blood flow after adrenaline injection did also not found important problems or complications.[10,13] Of note is that in most studies, patients suffering from vascular diseases were excluded.[10,12-13,18] Therefore, formally it cannot be concluded that the use of adrenaline in these patients is safe. However, as no cases involving ischemic complications after anaesthesia with lidocaine and adrenaline have been reported in the last 60 years, also the risk in these patients, if present, seems to be rather small.

While this manuscript was in preparation, a similar systematic review study was published supporting our findings.[26] Hence it seems likely that the ancient dogma preventing the use of adrenaline in local anaesthesia involving distal extremities should be revised. As many procedures and therapies are based on empirical thoughts and reasoning, we foresee that many similar ancient dogmas might be subject to change in an era of evidence based medicine.

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References

1. *Koller C. On use of Cocaine for producing anesthesia of eye. . Lancet. 1884; 4: 990-992.*
2. *Ruetsch Y.A., Boni T., Borgeat A. From cocaine to ropivacaine: the history of local anesthetic drugs. Curr Top Med Chem. 2001; 1: 175-182.*
3. *Biscoping J., Bachmann-Mennenga M.B. [Local anesthetics from ester to isomer]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2000; 35: 285-292.*
4. *Yagiela J. Local anesthetics: A century of progress. Anesth Prog. 1985; 32: 47-56.*
5. *Marx J. ed. Rosen's emergency medicine : concepts and clinical practice 7th ed. Philadelphia: Mosby.2010.*
6. *Auletta MJ G.R. ed. Local Anesthesia for Dermatologic Surgery. New York: Churchill Livingstone.1991.*

7. *McCarthy J. ed. Plastic Surgery. Philadelphia: Saunders.1990.*
8. *Wilhelmi B.J., Blackwell S.J., Miller J.H., et al. Do not use epinephrine in digital blocks: myth or truth? Plast Reconstr Surg. 2001; 107: 393-397.*
9. *Andrades P.R., Olguin F.A., Calderon W. Digital blocks with or without epinephrine. Plast Reconstr Surg. 2003; 111: 1769-1770.*
10. *Sonmez A., Yaman M., Ersoy B., et al. Digital blocks with and without adrenalin: a randomised-controlled study of capillary blood parameters. J Hand Surg Eur Vol. 2008; 33: 515-518.*
11. *Altinyazar H.C., Demirel C.B., Koca R., et al. Digital block with and without epinephrine during chemical matricectomy with phenol. Dermatol Surg. 2010; 36: 1568-1571.*
12. *Chowdhry S., Seidenstricker L., Cooney D.S., et al. Do not use epinephrine in digital blocks: myth or truth? Part II. A retrospective review of 1111 cases. Plast Reconstr Surg. 2010; 126: 2031-2034.*
13. *Altinyazar H.C., Ozdemir H., Koca R., et al. Epinephrine in digital block: color Doppler flow imaging. Dermatol Surg. 2004; 30: 508-511.*
14. *Denkler K. A comprehensive review of epinephrine in the finger: to do or not to do. Plast Reconstr Surg. 2001; 108: 114-124.*
15. *Harness N.G. Digital block anesthesia. J Hand Surg Am. 2009; 34: 142-145.*
16. *Katis P.G. Epinephrine in digital blocks: refuting dogma. CJEM. 2003; 5: 245-246.*
17. *Lalonde D.H., Lalonde J.F. Discussion. Do not use epinephrine in digital blocks: myth or truth? Part II. A retrospective review of 1111 cases. Plast Reconstr Surg. 2010; 126: 2035-2036.*
18. *Lalonde D., Bell M., Benoit P., et al. A multicenter prospective study of 3,110 consecutive cases of elective epinephrine use in the fingers and hand: the Dalhousie Project clinical phase. J Hand Surg Am. 2005; 30: 1061-1067.*
19. *Singh T., Randhawa S., Khanna R. The EpiPen and the ischaemic finger. Eur J Emerg Med. 2007; 14: 222-223.*
20. *Kaspersen J., Vedsted P. [Accidental injection of adrenaline in a finger with EpiPen]. Ugeskr Laeger. 1998; 160: 6531-6532.*
21. *Velissariou I., Cottrell S., Berry K., et al. Management of adrenaline (epinephrine) induced digital ischaemia in children after accidental injection from an EpiPen. Emerg Med J. 2004; 21: 387-388.*
22. *Hinterberger J.W., Kintzi H.E. Phentolamine reversal of epinephrine-induced digital vasospasm. How to save an ischemic finger. Arch Fam Med. 1994; 3: 193-195.*
23. *Janssen R.L., Roeleveld-Versteegh A.B., Wessels-Basten S.J., et al. [Auto-injection with epinephrine in the finger of a 5-year-old child]. Ned Tijdschr Geneeskd. 2008; 152: 1005-1008.*
24. *Burkhart K.K. The reversal of the ischemic effects of epinephrine on a finger with local injections of phentolamine. J Emerg Med. 1992; 10: 496.*
25. *McCauley W.A., Gerace R.V., Scilley C. Treatment of accidental digital injection of epinephrine. Ann Emerg Med. 1991; 20: 665-668.*
26. *van Rijt W.G., de Wildt R.P., Tellier M.A. [Local anaesthetics containing epinephrine for use in the hand and fingers]. Ned Tijdschr Geneeskd. 2014; 158: A7390.*

Which operative technique for fixating complex distal radius fractures is safest, regarding iatrogenic damage to the superficial branch of the radial nerve? *A systematic review*

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Abstract

Objective: **This systematic review investigates three commonly used operative techniques for fixating complex distal radius fractures, regarding iatrogenic complications to the superficial radial nerve (SRN).**
Methods: **PubMed was consulted for English studies on the treatment of complex wrist fractures and postoperative complications to the SRN. The GRADE method was used to determine the quality of evidence.**
Results: **Thirteen studies were included. The Kischner wire technique (n=341) in-duced 39 - 41 (11,4 – 12,0 %) complications to the SRN. Fixation with plates and screws (n=100) induced 7 - 12 (7 – 12 %) complications to the SRN. Pin fixation (n=160) induced 6 – 8 (3,8 – 5,0 %) complications to the SRN. In ten studies the level of evidence was low, three studies had a very low level of evidence.**
Conclusion: **A trend was observed towards pin fixation as the safest technique for fixating complex wrist fractures, limiting iatrogenic complications to the SRN. Data from randomized clinical trials which would provide more reliable evidence is current-ly lacking.**

Introduction

The superficial radial nerve (SRN) is a sensory branch of the more proximal radial nerve. It rises from the dorsal side of the wrist, between the tendons of the brachi-oradialis and the extensor carpi radialis longus (ECRL) muscles. After the SRN pierces the antebrachial fascia it continues superficially towards the anatomical snuffbox. Distal to this point, the SRN proceeds to the dorsum of the radial side of the hand.[1]

Considering the importance of the sensory function of the human hand, the SRN must be treated with care. Another important point of concern is its vulnerability in trauma and iatrogenic injury.[2] Studies show an iatrogenic SRN injury in 0 - 20 % of the fixation operations in wrist fractures.[3-15] These operations include Kischner wire (K-wire) fixation, pin fixation and fixation with plates and screws. Symptoms of SRN injury are pain, painful neuromas which are very difficult to treat, loss of sensation[16] and paraesthesia.[17]

Depending on the complexity of the fracture, surgeons use different approach-es to fixate wrist fractures. Simple fractures of the distal radius, which implies a bone fracture without soft tissue damage requires no surgery. Treatment consist of plaster cast fixation. Complex fractures include distal radius fractures with damage to the surrounding soft tissue, intra-articular damage or bone fragments and can be treated in different ways. The use of K-wires is relatively easy and quick. However, the fixa-tion is not rigid and therefore, patients often need a plaster cast for several weeks. Also, the wires have an open connection with the external environment, which in-creases the possibility of infection. Fixation by plates and screws is a more difficult technique, which requires more operating skills and time .A great advantage is a quicker recovery and a reduction of potential stiffness. The latter also has its con-struct completely buried under the skin, which reduces the risk of infection. A disad-vantage is the possibility of damaging tendons, vessels and nerves. Pin fixation is normally used in combination with an external fixator. This enables the surgeon to treat very complex fractures, due to the versatile character of pins and external fixa-tion. Preoperative and long-term planning are essential to the success of this tech-nique, which makes it more extensive. Another disadvantage is the open connection with the external environment, which increases the possibility of infection.[18] Pin fixation is described as a safe and effective technique, for it should avoid damage to vital structures.[19]

In this review these three commonly used fixation techniques for complex dis-tal radius fractures are compared to get an insight into the best approach regarding the prevention of damage to the SRN.

Methods

In search of clinical studies on wrist fractures and iatrogenic injury of the superficial radial nerve, PubMed was used up to January 2014. Main keywords in the search string were Radial nerve, Wrist injuries, Postoperative complications and Fracture fixation. The complete search string is shown in Appendix A.

Inclusion criteria

The studies had to meet the following inclusion criteria: (1) patients with wrist frac-tures who needed operative fixation, (2) the studies had to describe postoperative complications of the SRN (3) and had to be written in English.

Exclusion criteria

Exclusion criteria used were Humerus fractures, SRN injury by trauma, Cadaver studies, Non-clinical studies and Non-availability. Studies were regarded available if they could be retrieved using a student EUR-account (Erasmus University of Rotter-dam) or a student RUG-account (Medical University of Groningen).

After a search for clinical studies on PubMed, the studies were separated into several groups. Two reviewers (MdB and JS) carried out the selection procedure. No disagreements occurred and therefore no third independent reviewer was enquired. First the studies were in- or excluded based on title, then by abstract and full-text.

Two reviewers (MdB and JS) conducted the data extraction simultaneously. No disagreements occurred during the data extraction. The collected information in-cluded demographics (age and sex), type of fracture, intervention, follow-up and postoperative complications of the SRN.

Methodological quality determination

After the data extraction the quality of evidence of the inclu-ded studies was deter-mined. A few disagreements between the two reviewers occurred, but were closed by compromise. The level of evidence was graded by using the Grades of Recom-mendation, Assessment, Development and Evaluation (GRADE), a score for quality of evidence and the strength of recommendations.[20] To get more insight in using the GRADE method, an publication by Goldet et al. was used[21] The GRADE score was used for all studies. The following GRADE criteria were used: type of evidence, serious or very serious limitation to study quality, important inconsistency, some or major uncertainty about directness, imprecise or sparse data, high probability of re-porting bias (selective data reporting), strong evidence of association-significant rela-tive risk of > 2 based on consistent evidence from two or more observational studies, with no plausible confounders, very strong evidence of association-significant relative risk of > 5 based on direct evidence with no major threats to validity, evidence of a dose response gradient. All plausible confounders would have reduced the effect.

First the type of evidence was determined. Every other criterion could either de-crease or increase the GRADE score. Based on the maximum (+4) and minimum (-7) possible score, four groups were categorized: Group A (4, 3 or 2 points), group B (1, 0 or -1 point), group C (-2, -3 or -4 points) and group D (-5, -6 or -7 points). Combin-ing the type of evidence and the categorized group, studies were divided into four different levels of quality: high: further research is very unlikely to change our confi-dence in the estimate of effect. Moderate: Further research is likely to have an im-portant impact on our confidence in the estimate of effect and may change the esti-mate. Low: Further research is very likely to have an important impact on our confi-dence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Results

The primary search for studies in the database of PubMed resulted in 30 potentially relevant studies of which 13 were used for final analysis (Figure 1).

Figure 1- Flowchart of the literature

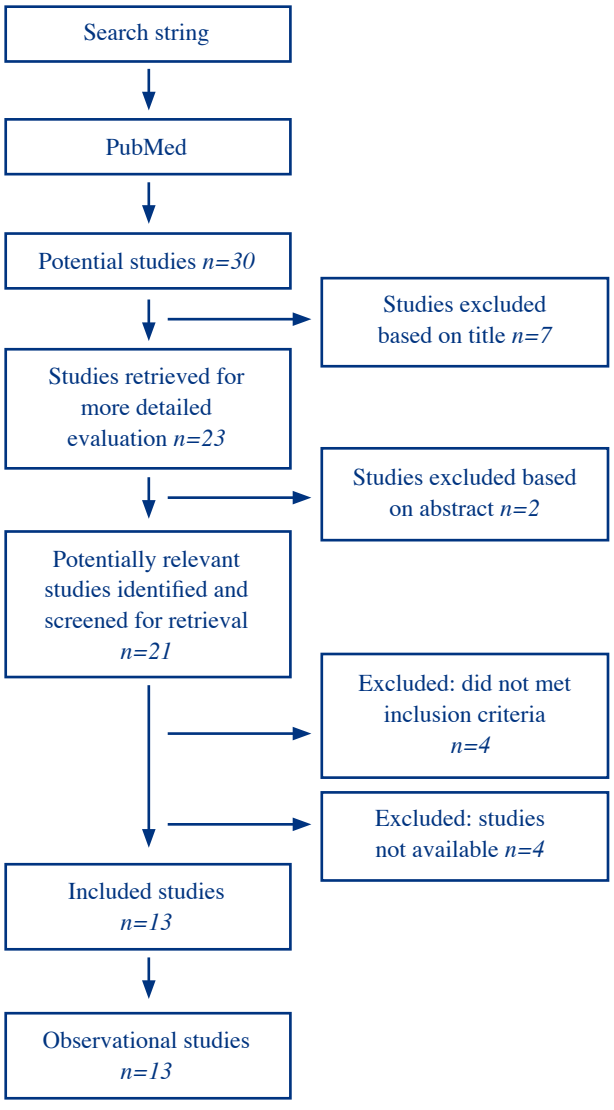

Table 1 - Data extraction of the included studies, characteristics of the study population

Author	Treatment group	Fracture type	Age (year)	Sex	Fixation technique	Control group
Emami A et al.[11]	40 patients	Unknown	Unknown	Unknown	2 half pins	-
Fritz T et al.[3]	109 patients	70 % extra-articular	mean 64	21% men	3 K-wires	-
	110 fractures	30 % intra-articular		79% women		
Mirza A et al.[8]	21 patients	Unknown	mean 54	8 men	Cross K-wire fixation with	-
			(27 – 87)	13 women	external fixator	
Singh S et al.[12]	40 patients	Unknown	Unknown	Unknown	K-wire	-
Lee HC et al.[7]	22 patients, 3 patients	4 extra-articular	mean 44,6	11 men	AO Titanium T-plate	-
	received T-plate	18 intra-articular*	(20 – 70)*	11 women*		
Habernek H et al.[15]	80 patients	30 extra-articular	mean 62.5 (men)	10 men	3 – 4 K-wires	-
		50 intra-articular	55 (women)	70 women		
Chen Y et al.[9]	53 patients	Unknown	mean 47,4	24 men	4 pins and 1 – 3 K-wires	-
			(18 – 77)	29 women		
Anderson JT et al.[4]	24 patients	3 extra-articular	mean 53.8	7 men	AO external fixator n = 24	-
		18 intra-articular	(21 – 91)*	17 women*	Combined with:	
		3 unknown*			Open pin placement n = 23	
					K-wire n = 14	
					Allograft bone n = 3	
					Volar buttress plate n = 1	
					K-wire and bonegraft n = 2	
					K-wire, bonegraft and volar	
					buttress plate n = 1	
Tyllianakis M et al.[14]	20 patients	8 extra-articular	mean 53,5	7 men	2 K-wires and 1 half pin	-
	21 fractures	13 intra-articular	(39 – 65)	13 women	and two full circular rings	
Krukhaug Y et al.[5]	29 patients	29 intra-articular	median 48	26 men	AO π plate	-
			(22 – 74)	6 women		
Abbaszadegan H et	47 patients	47 extra-articular	mean 63	11 men	Hoffman-pins (n = 23)	Plaster cast
al.[6]			(22 – 75)	36 women		(n = 24)
	36 patients	36 extra-articular	16+	28 men	AO-plate	-
Moore TM et al.[10]				8 women		
	78 patients, 30 distal	9 extra-articular	mean 24	70 men	ASIF compression plate	-
Dodge HS et al.[13]	radius fractures	21 intra-articular*	(13 – 59)*	8 women*		

*Exact data about the three patients treated with intended treatment unknown.

The discussed techniques in these studies were K-wires[3,4,8,9,12,14,15], plates and screws[4,5,7,10,13] and pin fixation.[4,6,9,11,14]

The characteristics of the study population and outcome are shown in table 1 and table 2, respectively.

In this review several studies on fixating distal radius fractures and postopera-tive complications to the SRN were compared. The K-wire technique was conducted on 341 fractures and induced 39 - 41 (11,4 – 12,0 %) complications to the SRN. From these SRN complications 8 (19,5 – 20,5 %) resolved. Complications to the SRN included (partial) loss of sensitivity (n=8), pain (n=5), paraesthesia (n=26) and neuropathy (n=2). (Table 2)

The usage of plates and screws was performed on 100 distal radius fractures and induced 7 - 12 (7 – 12 %) complications to the SRN. From these SRN complications 2 (16,7 – 28,6 %) resolved. Complications to the SRN included (partial) loss of sensi-tivity (n=7), pain (n=2), neuropathy (n=2) and unknown (n=1). (Table 2)

Pin fixation was conducted on 160 fractures and induced 6 – 8 (3,8 – 5,0 %) compli-cations to the SRN, in which 4 (50 – 66,7 %) resolved. Complications to the SRN in-cluded (partial) loss of sensitivity (n=3), pain (n=3) and neuropathy (n=2) (Table 2).

After extracting the data from the included studies the quality of evidence was determined using the GRADE score. All observational studies started with a low score.[20] After this, the studies were judged based on the criteria of the GRADE method and the studies were ranked based on their score and divided into four groups (Table 3). There were no studies with a high score (group A). Ten studies with a moderate score were categorized in group B. Three studies with a low score were categorized in group C. There were no studies with a very low score (group D).

The quality of evidence was determined combining the GRADE score with the type of evidence. This resulted in ten studies with a low score and three studies with a very low score.

No methodological differences between the three operative techniques were observed.

Table 2 - Data extraction of the included studies, outcome

Author	Outcome measure	Follow-up	Results	Results by outcome measure
Emami A et al.[11]	Complications SRN		-	No complications to SRN
Fritz T et al.[3]	Complications SRN	23 months	-	Paraesthesia (partly) n = 13
		(15 – 48) n = 72		No resolving mentioned
Mirza A et al.[8]	Complications SRN	20 months	-	Sensibility of SRN resolved to mild sensitivity
		(12 – 36)		without functional compromise n = 1
Singh S et al.[12]	Complications SRN	5 months	-	Complete sensory loss n = 4
		(3 – 9)		Reduced two point discrimination (>4 mm) n = 2
				Painful neuroma n = 2
Lee HC et al.[7]	Complications SRN	12,6 months	-	Numbness of SRN distribution n = 3*
Habernek H et al.[15]	Complications SRN	1 year	-	Paraesthesia n = 12 (resolved n = 6)
Chen Y et al.[9]	Complications SRN	3 – 6 months	-	Reduced sensation two point discrimination = 1
				(resolved in 4 months)
				Numbness n = 1 (resolved in 4 months)
Anderson JT et al.[4]	Complications SRN	6,5 months	-	Neuropathy n = 2*
		(2 – 14)		
Tyllianakis M et al.[14]	Complications SRN	12,5 months	-	Irritation n = 3 (resolved in 3 months n = 1)
		(11 -14)		
Krukhaug Y et al.[5]	Complications SRN	Mean 23 months	-	Neuroma n = 1
Abbaszadegan H et	Complications SRN	1 year n= 46	-	Sensory disturbance n = 1 (resolved)
al.[6]	Complications SRN	Mean 2.5 years	-	Neuroma n= 1
Moore TM et al.[10]		(1.5 – 7)		Loss of sensation n = 4 (resolved n = 2)
				Unknown n = 1
	Complications SRN	Mean 29 months	-	No complications to SRN
Dodge HS et al.[13]		(5 – 51)		

*Not mentioned if these complications occurred on patients treated with intended treatment

Table 3 - Quality of evidence by GRADE score

Author	Type of Evidence	Limitation to study quality	Important inconsis-tency	Uncer tainty about directness	Imprecise or sparse data	Reporting bias	Strong evidence of associ-ation	Dose response gradient	Adjusted for con-founders	Group	Quality of evidence
Emami A et al.[11]	Low	-2	0	-1	-1	-1	+1	0	0	C	Very low
Fritz T et al.[3]	Low	-1	0	0	0	0	+1	0	0	B	Low
Mirza A et al.[8]	Low	0	0	0	0	0	+1	0	0	B	Low
Singh S et al.[12]	Low	-1	0	0	-1	0	0	0	0	C	Very low
Lee HC et al.[7]	Low	-1	0	-1	0	0	0	0	0	C	Very low
Habernek H et al.[15]	Low	0	0	0	0	0	+1	0	0	B	Low
Chen Y et al.[9]	Low	-1	0	0	0	0	+1	0	0	B	Low
Anderson JT et al.[4]	Low	-1	0	0	0	0	0	0	0	B	Low
Tyllianakis M et al.[14]	Low	0	0	0	0	0	+1	0	0	B	Low
Krukhaug Y et al.[5]	Low	0	0	0	0	0	+1	0	0	B	Low
Abbaszadegan H et al.[6]	Low	-1	0	0	0	0	+1	0	0	B	Low
Moore TM et al.[10]	Low	0	0	0	0	0	+1	0	0	B	Low
Dodge HS et al.[13]	Low	0	0	0	0	0	+1	0	0	B	Low

Discussion

In this systematic review, three commonly used techniques for fixating wrist fractures and their risk of complications to the SRN are compared. We included thirteen stud-ies, which were all observational.

During data extraction a discrepancy in outcome measures occurred. This dis-crepancy between the number of complications is caused by the studies of Anderson J.T. et al.[4] and Lee H.C. et al.[7], who did not mention which techniques caused complications to the SRN. In these studies several fixating techniques are described separately and in the study by Anderson J.T. et al.[4] also several combinations were used.

Because of a lack of confidence intervals and P-values in the included studies, no statistic analyses could be performed.

By using the GRADE score we assessed the methodological quality of the studies. The quality of evi-dence of the reviewed studies was questionable. IThis is partly explained by the absence of randomized clinical trials (RCT's).

A concern is the small number of retrieved studies. We were unable to find RCT's who compare two different operative techniques for fixating complex distal radius fractures.

Conclusion

Considering the lack of good quality studies, we could not determine an optimal fixa-tion technique regarding the prevention of complications to the SRN. However, based on our data, a trend towards pin fixation being the safest technique for fixating com-plex wrist fractures is present. Pin fixation did not only induce the lowest incidence of complications in absolute numbers, but also showed the highest rate of resolving complications of the SRN. More research has to be done to determine whether pin fixation can be considered best and if pin fixation is best for all types of distal radial fractures. High quality RCTs are needed.

Appendix A

Used search string: ((((“Wrist Joint”[Mesh]) OR “Radius”[Mesh]) OR “Radius Frac-tures”[Mesh]) OR “Wrist Injuries”[Mesh]) AND ((((((“Fracture Fixation”[Mesh]) OR “Fracture Fixation, Internal”[Mesh]) OR “Bone Nails”[Mesh]) OR “Bone Wires”[Mesh]) OR “External Fixators”[Mesh]) OR “Bone Plates”[Mesh]) AND (((((“Radial Nerve”[Mesh]) OR “Radial Neuropathy”[Mesh]) OR “Postoperative Complications”[Mesh]) OR “Nerve Compression Syndromes”[Mesh]) OR “superficial radial nerve”) AND (((complication*) AND “radial nerve”) OR “superficial radial nerve”) NOT ((((“Elbow Joint”[Mesh]) OR “Elbow”[Mesh]) OR “Humerus”[Mesh])] AND English [lang]

References

1. *Auerbach D.M., Collins E.D., Kunkle K.L., et al. The radial sensory nerve. An anatomic study. Clin Orthop Relat Res. 1994: 241-249.*
2. *Robson A.J., See M.S., Ellis H. Applied anatomy of the superficial branch of the radial nerve. Clin Anat. 2008; 21: 38-45.*
3. *Fritz T., Wersching D., Klavora R., et al. Combined Kirschner wire fixation in the treatment of Colles fracture. A prospective, controlled trial. Arch Orthop Trauma Surg. 1999; 119: 171-178.*
4. *Anderson J.T., Lucas G.L., Buhr B.R. Complications of treating distal radius fractures with external fixation: a community experience. Iowa Orthop J. 2004; 24: 53-59.*
5. *Krukhaug Y., Hove L.M. Experience with the AO Pi-plate for displaced intra-articular fractures of the distal radius. Scand J Plast Reconstr Surg Hand Surg. 2004; 38: 293-296.*
6. *Abbaszadegan H., Jonsson U. External fixation or plaster cast for severely displaced Colles’ fractures? Prospective 1-year study of 46 patients. Acta Orthop Scand. 1990; 61: 528-530.*
7. *Lee H.C., Wong Y.S., Chan B.K., et al. Fixation of distal radius fractures using AO titanium volar distal radius plate. Hand Surg. 2003; 8: 7-15.*
8. *Mirza A., Jupiter J.B., Reinhart M.K., et al. Fractures of the distal radius treated with cross-pin fixation and a nonbridging external fixator, the CPX system: a preliminary report. J Hand Surg Am. 2009; 34: 603-616.*
9. *Chen Y., Zheng X., Wang J., et al. Reliable techniques to avoid damaging the superficial radial nerve due to percutaneous Kirschner wire fixation of the distal radius fracture through the radial styloid process. Surg Radiol Anat. 2010; 32: 711-717.*
10. *Moore T.M., Klein J.P., Patzakis M.J., et al. Results of compression-plating of closed Galeazzi fractures. J Bone Joint Surg Am. 1985; 67: 1015-1021.*
11. *Emami A., Mjoberg B. A safer pin position for external fixation of distal radial fractures. Injury. 2000; 31: 749-750.*
12. *Singh S., Trikha P., Twyman R. Superficial radial nerve damage due to Kirschner wiring of the radius. Injury. 2005; 36: 330-332.*
13. *Dodge H.S., Cady G.W. Treatment of fractures of the radius and ulna with compression plates. J Bone Joint Surg Am. 1972; 54: 1167-1176.*
14. *Tyllianakis M., Mylonas S., Saridis A., et al. Treatment of unstable distal radius fractures with Ilizarov circular, nonbridging external fixator. Injury. 2010; 41: 306-311.*
15. *Habernek H., Weinstabl R., Fialka C., et al. Unstable distal radius fractures treated by modified Kirschner wire pinning: anatomic considerations, technique, and results. J Trauma. 1994; 36: 83-88.*
16. *Linscheid R.L. Injuries to radial nerve at wrist. Arch Surg. 1965; 91: 942-946.*
17. *Pirela-Cruz M.A., Scher D.L. Exposure of distal radius fractures using a direct radial approach with mobilization of the superficial branch of the radial nerve. Tech Hand Up Extrem Surg. 2010; 14: 218-221.*
18. *Hull P., Baraza N., Gohil M., et al. Volar locking plates versus K-wire fixation of dorsally displaced distal radius fractures--a functional outcome study. J Trauma. 2011; 70: E125-128.*
19. *Behrens F. General theory and principles of external fixation. Clin Orthop Relat Res. 1989: 15-23.*
20. *Atkins D., Best D., Briss P.A., et al. Grading quality of evidence and strength of recommendations. Bmj. 2004; 328: 1490.*
21. *Goldet G., Howick J. Understanding GRADE: an introduction. J Evid Based Med. 2013; 6: 50-54.*

Glomerular diseases for dummies

A Clinical Lesson

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Box 1. Overview A literature overview answering the following questions:

- When to consider the involvement of glomerular disease
- Are there different types of Glomerular disease?
- Which glomerular diseases should be considered when there is isolated haematuria?
- Which glomerular disease should be considered when there is isolated proteinuria?
- Does the amount proteinuria help my diagnoses?
- Does the combination of haematuria and proteinuria help my diagnosis?
- Does the patient's age help you differentiate between glomerular diseases?
- Do extra renal symptoms help us in the diagnosis?
- How can serology help us in our diagnosis?
- When do we see hypocomplementemia?
- Does the progression of the disease and the accompanying creatinine levels help us in our diagnoses?
- When is a kidney biopsy indicated?
- Are there contra-indications for a biopsy?

Introduction

Students and beginning doctors often find it difficult to navigate through the vast amount of glomerular diseases and their diverse causes and presentations. This makes it difficult for them to make a differential diagnosis. It can, however, be of great importance to quickly be able to differentiate between several groups of glomerular disease, especially in diseases with an acute onset and progression. Delay of treatment can cause permanent damage to the kidneys and higher treatment cost.[1]

When considering a glomerular disease, specific renal symptoms can be a sign of glomerular damage. Symptoms such as haematuria, foamy urine, oedema, anaemia, changes in the colour and smell of urine are signs of a renal component in the patient's possible disease.[2] Glomerular diseases are often discovered in general health screenings because the proteinuria or haematuria accompanying the disease are usually asymptomatic in onset.[3] However, glomerular disease can have an acute presentation.[2] To further confirm renal involvement, the presence of haematuria and serum creatinine can be determined. One should note that these values do not always deviate from a normal range in glomerular diseases.[2]

Another aspect that could be observed is the amount of erythrocytes and protein in the urine. Haematuria is often a symptom of renal and glomerular diseases, but haematuria can also be a symptom of damage in the lower urinary tract. However, if more than 40% of the erythrocytes in the urine are dysmorphic in shape, mainly acanthocytes, or if erythrocyte casts can be found in the urine, a glomerular disease is likely. [4,5] Loss of albumin or larger serum proteins in the urine is a typical symptom of glomerular disease.[4]

One should keep in mind that there are many systemic diseases that have a secondary focus in the kidney and that not all of these patients will have kidney problems. It is however possible that systemic (autoimmune) disease can lead to, or has already caused, kidney damage.[2] Systemic disease may also present primarily with kidney involvement. It is very important to recognize these systemic syndromes because it may influence the diagnosis and prognosis of the patient.

This overview of recent literature aids the inexperienced in making a differential diagnosis when suspecting glomerular disease in a patient. We have attempted to categorize the glomerular diseases by utilizing clinical symptoms and results of diagnostic tests based on recent literature. This overview will quickly give the reader insight in which diseases could fit a patient's clinical presentation.

In this review we discuss the most common glomerular diseases such as membranous nephropathy, minimal change disease, rapidly progressive glomerulonephritis, focal segmental glomerulosclerosis, IgA nephropathy and diabetic nephropathy and the glomerular diseases caused by hereditary predisposition, infections, vasculitides, systemic diseases and auto-immune diseases.

Which glomerular diseases should be considered when there is isolated haematuria?

Haematuria can occur in some cases of glomerular disease. Haematuria is determined by using a dipstick. When speaking of isolated haematuria one can differentiate between macroscopic and the more common microscopic haematuria.[2] Microscopic haematuria can only be determined using a microscope or a dipstick and has a prevalence of 2.5% in the overall population.[3] The most common glomerular causes of isolated haematuria among patients younger than 40 are IgA nephropathy and thin basement membrane disease. [3] Alport's disease can also present with haematuria and progressive proteinuria at a young age.[7] The haematuria in IgA nephropathy and Alport's disease can be both microscopic as well as macroscopic.[7,8,9] Other important glomerular diseases presenting with haematuria are the diseases in the group of rapidly progressive glomerulonephritis, but usually these diseases also have proteinuria.[10]

Which glomerular disease should be considered when there is isolated proteinuria?

Nephrotic diseases often present with proteinuria but without haematuria.[2] The most common glomerular diseases without haematuria are minimal change disease, focal segmental glomerulosclerosis and diabetic nephropathy. [2,10,11,12] Amyloidosis can present without haematuria as well.[11,12] The absence of isolated haematuria allows us to exclude several diseases: IgA nephropathy always presents with haematuria and if boys below the age of 10 do not develop haematuria, the diagnosis of Alport's syndrome is highly unlikely. [7,8]

The presence of proteinuria is to be determined by using a dipstick. When the dipstick is positive, there is an indication to determine the protein concentration in a single urine sample or a 24-hours urine collection. Less than 150 mg of protein in the 24-hours urine is considered normal.[2]

Does the amount of proteinuria help reach a diagnosis?

Proteins in the urine are often a sign of glomerular damage and the amount of proteinuria can help differentiate between glomerular diseases. Proteinuria of more than 3.5 grams a day is called nephrotic proteinuria.[2] Nephrotic proteinuria can lead to the nephrotic syndrome which involves oedema and hypoalbuminemia.[2] According to Koening and Bolton the nephrotic syndrome in adults is caused by membranous nephropathy (MN) in 33% of the cases, focal segmental glomerulosclerosis (FSGS) in 33%, IgA nephropathy in 10%, minimal change disease (MCD) in 15% and membranoproliferative glomerulonephritis (MPGN) in 2-5%.[1] Although the amount of protein narrows the differential diagnosis, it might not help to differentiate between these underlying diseases. MN for example, can also be caused by many underlying diseases.[1] The absence of symptoms of the nephritic syndrome, including edema and hypoalbuminaemia, in a patient with nephrotic range proteinuria may point toward an secondary FSGS as a feature of chronic renal damage and hyperfiltration.

Does the combination of haematuria and proteinuria help in finding a diagnosis?

Most glomerular diseases present with a combination of both haematuria and proteinuria.[10] Therefore it is difficult to exclude certain diseases from the differential diagnosis based on the combination haematuria and proteinuria exclusively. The combination of proteinuria and haematuria is often seen when (extrarenal) infection is involved.[10] We can however differentiate between the nephrotic syndrome with or without haematuria. The previous question showed that MN, FSGS, MCD, IgA Nephropathy and MPGN are the most common causes of the nephrotic syndrome.[10] FSGS and MCD commonly present without haematuria but MN, IgA and MPGN can present with haematuria, which makes these diseases more likely.[10] Clinical suspicion based on these two symptoms is often not enough to confirm a diagnosis.[10]

Does the patient's age help differentiate between glomerular diseases?

Age is a helpful characteristic when differentiating between glomerular diseases.[10] Infection related glomerulonephritis is a disease that often presents itself shortly after a throat or skin infection in children between the age of 5 and 12 years old.[13] Another example is the classic children's disease: the haemolytic uremic syndrome (HUS). Diarrhoea associated HUS mainly presents in young children who have had an Escherichia coli which produces Shiga toxin or streptococcus pneumonia infection. It is one of the most important causes of acute kidney disease in children and is important to be recognised promptly.[14] The most common cause of glomerular disease and nephrotic syndrome among children is the minimal change disease (MCD).[2]

Table 1 - The differential diagnosis dependent on age and presentation.

Age (years)	Nephrotic syndrome	Mild glomerulonephritis	Moderate-severe glomerulonephritis.
< 15	Minimal Change Disease (MCD), Focal segmental glomerulosclerosis (FSGS), Mesangial proliferative glomerulonephritis (MPGN) Membranous Nephropathy (MN),	Mild post-infectious glomerulonephritis, IgA nephropathy, thin basement membrane disease, hereditary nephritis, Henoch-Schönlein purpura (mesangial proliferative glomerulonephritis)	Post-infectious glomerulonephritis, membranoproliferative glomerulonephritis
15-40	FSGS, MCD, diabetic nephropathy, preeclampsia, post-infectious glomerulonephritis	IgA nephropathy, thin basement membrane disease, lupus nephritis (SLE), hereditary nephritis (Alport's disease), mesangial proliferative glomerulonephritis	Post-infectious glomerulonephritis, lupus nephritis, rapidly progressive (crescentic) glomerulonephritis, IgA nephropathy,
>40	FSGS, MN, diabetic nephropathy, MCD (age >60 years), IgA nephropathy, primary amyloidosis (or the related disorder light chain deposition disease).	IgA nephropathy	fibrillary glomerulonephritis, membranoproliferative glomerulonephritis Rapidly progressive glomerulonephritis, vasculitis (including mixed cryoglobulinemia), IgA nephropathy, fibrillary glomerulonephritis, post-infectious glomerulonephritis

Source: differential diagnosis of glomerular disease, Uptodate [8]

In adults however, membranous and diabetic nephropathy are the most common underlying causes of the nephrotic syndrome.[24,25] At older ages it is essential to consider malignancies as cause of glomerular disease. In patients, older than 60, light-chain deposition disease is the cause of the nephrotic syndrome in 15-20% of cases. Light chain deposition disease is common among patients with multiple myeloma or lymphoma.[27] Table 1 summarizes how the differential diagnosis of the nephrotic syndrome, mild glomerular nephritis (in which kidney function is normal) and moderate to severe glomerular nephritis (in which kidney function is impaired) differs between several age groups.[10,26]

What is the importance of recognising extrarenal symptoms?
It is important to conclude whether the glomerular disease is associated with a systemic disease before considering a primary glomerular disease. Extrarenal symptoms, signs of illness in other organ systems, in combination with a kidney problem often indicate a systemic disease and therefore serve as an important diagnostic tool. The secondary causes of glomerular disease are divided into the following categories: Systemic autoimmune diseases, infections, vasculitis, microangiopathy, diabetes mellitus and paraproteinaemia or amyloidosis. [6] Patients are usually diagnosed with these diseases before signs of renal involvement, but the disease can sometimes reveal itself as a renal disease.[6] Specific extrarenal symptoms will be discussed further on.

Which autoimmune diseases can cause glomerular disease?
The systemic autoimmune diseases that are associated with glomerular diseases are Systemic Lupus Erythematodes (SLE), several rheumatic diseases and cryoglobulinemia.[4] Patients with these disorders often exhibit typical symptoms in other organ systems such as joint pain, problems with mucous membranes, Raynaud's phenomenon, butterfly rash (SLE) and sclerosis of the skin and other organs [6] Especially SLE is a common cause of glomerulopathies and can present with different kinds of glomerulopathies.[5] Seventy percent of SLE patients develop glomerulopathy and forty percent presents with renal symptoms.[6] Autoimmunlogical phenomena can give a clue that there is an underlying systemic autoimmune disease (Box 2).[5]

Box 2. Autoimmunological phenomena

- (mouth) ulcers
- UV sensitivity
- Raynaud
- Hair loss
- Skin abnormalities
- Sicca symptoms
- Uveitis

Goodpasture's disease is a primary renal disease but may also present systemically causing haemoptysis, called Goodpasture's Syndroom, a pulmonary-renal syndrome.[20]

Which vasculitides may cause glomerular disease?
Vasculitides may also be associated with glomerular disease. The vasculitides associated with glomerular injury are granulomatosis with polyangiitis (GPA, also known as Wegener's disease), Micropolyangiitis (MPA), Eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss syndrome) and IgA vasculitis (IGAV, also known as Henöch-Schönlein disease).[4]

These disorders are small vessel vasculitides. A vasculitis in the kidney usually leads to damage of the wall of the capillary loop and extracapillary glomerulonephritis.[5] These vasculitides usually present with typical extra-renal symptoms.[29] There are often skin abnormalities but each type of vasculitides has his own typical symptoms. GPA for example also presents with extrarenal symptoms in the upper respiratory system and IgA vasculitides usually presents one week after an infection. Especially patients with GPA have a high percentage with renal involvement (90%). [29] When vasculitides are suspected one should specify the types according to their symptoms or perform further research, for example a biopsy.

What are clinical clues for microangiopathies?
The category microangiopathies as a secondary cause of glomerular diseases contains a variety of diseases such as haemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation, malignant hypertension, as well as pre-eclampsia.[5] In these diseases or conditions damage occurs in the vascular endothelium and results in intimafibrosis and/or thrombus formation in the smaller arterioles and glomerular capillaries (thrombotic microangiopathy). HUS typically presents with petechiae, hematoma or signs of thrombotic microangiopathy and patients may have a positive family history. TTP can differentiate itself from HUS by neurologic symptoms.[5]

What is the presentation of Diabetic Nephropathy?
Diabetic nephropathy typically presents with a nephrotic syndrome with diffuse glomerulosclerosis in patients who have had DM for more than 15 years. The disorder often shows slow progression.[5,39] When considering the diagnosis of Diabetic Nephropathy (DN) it should be taken into account that other kidney diseases are not excluded in diabetic patients. In early onset of DN, the decline of renal function is masked by hyperfiltration.[5] Patients with DM are often screened for kidney damage, therefore DN is often found before it becomes symptomatic.

Patients with DM type 1 often already have retinopathy and high blood pressure when they present with diabetic nephropathy.[5] In patients with DM type 2 this may not be the case and will more often present with vague symptoms and abnormal course of disease. Sometimes DM type 2 may present itself with proteinuria.[5]

Which glomerular disease can be caused by paraproteinaemia and amyloidosis?

Patients with amyloidosis or paraproteinaemia can present with a nephrotic syndrome.

The diseases in this category which lead to glomerular problems are primary (AL, ALH, or rarely AH) amyloidosis, monoclonal immunoglobulin deposition diseases (MIDD; light chain deposition disease , heavy chain deposition disease , and light and heavy chain deposition disease) and miscellaneous glomerulopathies (monoclonal cryoglobulinemia, proliferative glomerulonephritis due to monoclonal IgG deposition).[27] One should note however, that these conditions can also cause tubular and interstitial diseases, such as cast nephropathy, that may lead to renal insufficiency as a result.[27]

A typical feature of multiple myeloma is the presence of monoclonal light chain immunoglobulins (Bence Jones protein) in the urine which are produced by the myeloma.[27] It is important to realise that Bence Jones proteins can give negative dipstick results even while there is proteinuria. This is because the dipstick only measures albumin . The 24-hours urine collection will however show pathologic amounts of proteinuria.[4]

In patients with proteinuria but with no protein found using a dipstick the presence of a paraprotein should be ruled out. Paraproteinemic renal disease should be specifically considered in older patients because the higher incidence of multiple myeloma and lymphoma.[27]

What are the hereditary components and other predisposing conditions (chronic infections) of glomerular disease?

Alport's disease is a genetic disorder and is inherited in a X-chromosomal fashion in 80% of the cases.[8] Patients with Alport's disease often present with sensorineural hearing loss and ocular abnormalities.[8] Alport's disease is a glomerular disease as a result of a change in the collagen structure of the glomerular basement membrane (GBM), which is caused by a defect in the gene encoding for one of the chains of collagen IV. Because of the gene defects the permeability of the GBM changes which results in haematuria and proteinuria.[6]

Other causes of glomerular problems are certain (chronic) infections such as hepatitis and HIV. Hepatitis B, for example, can cause polyarteritis nodosa and membranous glomerulopathy. HCV often presents with a membranoproliferative glomerulonephritis.[28] However, not all these patients develop glomerular problems.[28]

HIV associated nephropathy (HIVAN) is often expressed as a focal sclerosing glomerulosclerosis (FSGS) associated with tubular micro cysts and interstitial inflammation.[29] The classic presentation of HIVAN, almost exclusively occurring in blacks, is often accompanied by significant proteinuria and rapidly progressive kidney disease with normal blood pressure and normal enlarged kidneys.

How can serology help reach a diagnosis?

Serology is a useful tool that will help us differentiating between several glomerular diseases. With serology it is possible to identify antibodies in the serum. Examples of relevant antibodies are: ANCA (Anti neutrophil cytoplasmic antibody), ANA (antinuclear antibodies) and anti-double-stranded DNA antibodies and antibodies directed at certain infections such as HBV, HCV and HIV.[10,16,17] The serum complement levels can be measured as well, but we will discuss this further below.

A combination of ANA antibodies and hypocomplementemia is suspicious for SLE. But even in the case of SLE, because the subtype of glomerulonephritis can only poorly be predicted, it is necessary to perform renal biopsy, because each subtype requires different treatment.[18] ANCA antibodies are measurable in patients with one of the many vasculitides such as granulomatosis with polyangiitis (GPA, Wegener's disease), microscopic polyangiitis, Churg-Strauss, renal-limited vasculitis and drug-induced vasculitis.[10,19]

When patients show signs of alveolar bleeding (haemoptysis) anti-GBM disease should be considered, but be aware that this disease can present without pulmonary involvement. The presence of Anti-GBM disease can be diagnosed utilizing serology alone. An ELISA is enough evidence to diagnose the disease.[20] The presence of anti-PLA2 receptor antibodies has a high specificity for primary membranous nephropathy in nephrotic patients and may render a renal biopsy unnecessary.[30]

It should be noted that serology usually cannot give a definite diagnosis and a renal biopsy is still the best way to reach a definite diagnosis in a patient with suspected glomerular disease.[10]

Complement levels as a new diagnostic tool?

Recent studies show that some glomerular diseases are associated with a shift in complement levels. The serum complement levels can be measured in the blood. Hypocomplementemia is common in several glomerulonephritic diseases such as: Lupus nephritis, post-infectious glomerulonephritis, membranoproliferative glomerulonephritis and combined cryoglobulinemia.[10,21-23] The cause of hypocomplementemia is the rapid activation of complement by immune depositions which cannot be matched with novo-synthesis of complement.[10,22,23]

IgA nephropathy, fibrillary glomerulonephritis and membranous Nephropathy show less activation of complement and therefore maintain normal complement values unless the patient has SLE or HBV.[21,23]

Does the progression of the disease and the accompanying creatinine levels help us reach a diagnosis?

Progression of kidney disease can be observed by looking at several factors such as the urine production, the amount of excreted proteins and the serum creatinine. The serum creatinine can be used as an estimation of the glomerular filtration rate (GFR) and therefore as an estimation of kidney function.[4] It is not always possible to use the serum creatinine levels because the serum level has a wide reference range and can be influenced by other factors, such as muscle mass.[2]

Nephrotic syndromes that sometimes present with acute kidney failure are: concurrent acute tubular necrosis (especially in patient above 50 or with MCD), tubular injury in collapsing FSGS (idiopathic or HIV-associated), MCD with an acute interstitial nephritis (caused by NSAID use), cresentic

glomerulonephritis with membranous nephropathy and nephrotic syndrome due to immune complex depositions.[10]

Creatinine levels are more reliable in patients that have been monitored for a longer duration.[2] A fast (within days, weeks or months) increasing level of creatinine is a typical presentation of Rapidly progressive glomerulonephritis (RPGN). Because advanced RPGN leads to irreversible kidney damage, it is important to recognise RPGN in an early stage.[31] Rapidly progressive glomerulonephritis has a common presentation with acute macroscopic haematuria and oedema, but particularly presents itself with decreased kidney function which rapidly progresses in time[31,32]. It is necessary to identify whether a RPGN is possible considering the consequences, of failing to recognize the disease, are severe.[31,32]

There are diseases which present with mild symptoms and a normal kidney function. Especially IgA nephropathy, thin membrane disease and minimal change disease are diseases which can present very mildly.[10] Mild glomerulonephritis presents with a normal kidney function and normal creatinine levels. Mild glomerulonephritis can be caused (but not always) by IgA nephropathy, post-infectious glomerulonephritis, hereditary nephritis and lupus nephritis. However, these diseases do not always present with mild glomerulonephritis.[10] Table 1 shows the differential diagnoses of mild and moderate to severe glomerulonephritis.[10]

When is a kidney biopsy indicated?

A kidney biopsy is an important diagnostic tool in kidney disease and is often necessary to reach a final diagnosis. It is important to consider whether the result of the biopsy will influence treatment of the disease. It is only justified to perform a biopsy if the outcome will confirm diagnosis or influence the treatment.[9]

A biopsy should always be considered in context of the clinical symptoms and laboratory findings. This is important because a biopsy could incidentally be taken from a part of the kidney that is not affected by the disease, which could lead to a false negative biopsy (sample error).[33]

A biopsy is especially indicated in young adults with an idiopathic nephrotic syndrome. In this case, a biopsy can differentiate between MCD, FSGS or MN.[33] A biopsy should also be performed in patients with SLE and renal symptoms because SLE can lead to several different types of glomerular diseases.[18]

A renal biopsy can cause several serious complications. Bleeding is the primary complication of renal biopsy. Post-biopsy bleeding can occur at three sites: (1) into the collecting system, leading to microscopic or gross hematuria and possible ureteral obstruction; (2) underneath the renal capsule, leading to pressure tamponade and pain; or (3) into the perinephric space, leading to hematoma formation and a possibly large fall in hematocrit.[34,35] These complications may result in silent hematoma, hematuria (3.5%), erythrocyte transfusion(0.9%), angiographic intervention to control bleeding(0.9%), nephrectomy(0.02%) or even death (0.02%).

Risks factors for bleeding complications are hypertension (systolic pressure >130mmHg), age (>40 years) and of course coagulopathies.[35] Coagulopathies are therefore a contraindication for renal biopsy and the importance of the renal biopsy should be considered individually by case.[37]

Other complications of renal biopsy are pain lasting more than 12 hours (4%), arteriovenous fistulas (18%, chronic hypertension because of a large subscapular hematoma (rare), perirenal infection (0.2%) and rarely a punction of the liver, pancreas or spleen may occur.[36] Because of these complications, a solitary native kidney has been considered an absolute contraindication to percutaneous biopsy. The concern is that marked bleeding may lead to nephrectomy and loss of all of the patient's functioning renal mass.[37] If a renal biopsy is considered necessary when there is a solitary kidney, surgical biopsy can be considered.[36]

It is not necessary to perform a biopsy in patients with a very mild disease. A biopsy is also not indicated if proteinuria exists with less than 500 mg per day, if there is no haematuria, normal kidney function and no indications for systemic disease.[36,38]

Table 2 - Systemic autoimmune diseases

	SLE	Rheumatic diseases				Cryo-globulinemia
		Sclerodermia	*RA*	*Sjögren*	*MCTD*	
Characteristic aspects	- Butterfly rash - Chronic discoid lesions - Ulcers (oral & nasopharyngeal) - UV sensitivity - Arthritis (without erosions) - Serositis - Neurological disorders (epilepsy, psychosis) - Hematologic disorders - Immunologic disorders (anti-ds-DNA etc.) - Anti-nuclear antibodies	- CREST-syndrome - Raynaud's phenomenon - Symmetrical skin thickening - Skin abnormalities: depigmentation, telangiectasia	- Proximal joint pain	Sicca syndrome	- lopecia - Raynaud's phenomenon - Myalgia	Purpura in cold environments

Table 3 - Overview of vasculitides and their presentations

Vasculitides	GPA	EGPA	MPA	IgAV
Characteristic symptoms	- Necrotising vasculitis in upper respiratory tract - Sinusitis - Saddle nose - Affects tear ducts, ears and trachea (hoarseness)	- Heart muscle and/or coronary inflammation (>50%) - Period of unexplained asthma - No eye involvement	- Similar to GPA but often without or mild upper respiratory tract involvement	- Purpura with IgA deposits (skin biopsy) - Onset within several weeks after infection - Intestinal involvement - Primarily in children and young adults - Often self-limiting
Other relevant symptoms	- Moving arthralgia - Involvement of eyes (40%) - Skin abnormalities (30-70%): * Purpura * Ulcers * Granuloma * Blisters	- Nasal polyps with obstruction - Peripheral neuropathy (upper & lower limb – more often than GPA) - Skin abnormalities (similar to GPA) - Abdominal cramps	- Kidneys - Lungs (haemoptysis) - Peripheral neuropathy (lower limb) - Eyes (conjunctivitis and scleritis) - Skin (purpura, ulcers)	- (bloody) diarrhoea - Arthralgia - General malaise - Skin rash often on lower limbs, bottom, forearm
Renal problems (% of the patient population)	70 - 90 %	35 %	70 %	50%
Prevalence	1 : 8.000	1 : 80.000		Children and young adults

There are several cases in which a biopsy may be contraindicated. In children younger than 6, presenting with a nephrotic syndrome, a biopsy is redundant because in 90% of the cases the symptoms are caused by MCD.[33,38] When it is clear that the nephropathy is caused by medication, for example NSAIDs, this is a contraindication for a biopsy.[33] In patients with diabetes mellitus with a typical slow developing nephropathy a biopsy may not be necessary.[33]

Discussion

We have attempted to provide a useful guide that will aid students and young doctors when navigating through the large variety of glomerular diseases. Using a combination of established and recent literature we managed to separate several groups of diseases and their symptoms. By using the format in which the article is written, utilizing common questions that could arise in the clinic, we attempt to give clinicians a clear and categorized view of the large and intricate group of glomerular diseases.

We believe that our article will allow clinicians to quickly evaluate the likeliness of certain glomerular diseases and whether the patient possibly has a disease with an acute or critical onset. It is however important to mention that clinical suspicion will not lead to a definite diagnosis in the majority of cases. This article will help doctors create their differential diagnosis, but the conclusive diagnosis can, unfortunately, rarely be made without renal biopsy results.

It should be mentioned that we did not manage to include all existing glomerular diseases. Fibrillary glomerulopathy is a disease that we decided not to include based on the rarity of the disease. Furthermore, we summarized several rheuma related disorders as 'rheumatic disorders' because we considered the individual disease prevalence as too low.

This overview has been based on textbooks, UptoDate, other recent literature and clinical experiences. We emphasize that each patient should still be assessed individually.

References

1. *Madaio M.P., Harrington J.T. The diagnosis of glomerular diseases: acute glomerulonephritis and the nephrotic syndrome. Arch Intern Med. 2001; 161: 25-34.*
2. *Kumar P C.M. Kumar & Clark's Clinical Medicine. Edinburgh: Elsevier Saunders, 2009.*
3. *Kelly J.D., Fawcett D.P., Goldberg L.C. Assessment and management of non-visible haematuria in primary care. Bmj. 2009; 338: a3021.*
4. *Reitsma WD E.J., Overbosch D. Differentiele diagnostiek in interne geneeskunde: Bohn Stafleu van Loghum, 2005.*
5. *Meer van der J S.C., Berge ten RJM. Interne geneeskunde: Bohn Stafleu van Loghum,, 2005.*
6. *Kumar V A.A., Aster JC, Robbins SL. Robbin's basic pathology. Philadelphia: Elsevier Saunders, 2013.*
7. *Gubler M, Levy M, Broyer M, Naizot C, Gonzales G, Perrin D, Habib R; Alport's syndrome. A report of 58 cases and a review of the literature: Am J Med. 1981;70(3):493.*
8. *Kashtan CE. Alport syndrome. An inherited disorder of renal, ocular, and cochlear basement membranes. Medicine (Baltimore) 1999; 78:338.*
9. *Trachtman H, Weiss RA, Bennett B, Greifer I. Isolated hematuria in children: indications for a renal biopsy. Kidney Int 1984; 25:94.*
10. *Herbert LA P.S., Glassock RJ(Ed), Forman JP (Ed) Differential diagnosis and evaluation of glomerular disease. In: Waltham, MA: Wolters Kluwer; 2012*
11. *Praga M, Borstein B, Andres A, et al. Nephrotic proteinuria without hypoalbuminemia: clinical characteristics and response to angiotensin-converting enzyme inhibition. Am J Kidney Dis 1991; 17:330.*
12. *Fries JW, Mendrick DL, Rennke HG. Determinants of immune complex-mediated glomerulonephritis. Kidney Int 1988; 34:333.*
13. *Blyth CC, Robertson PW, Rosenberg AR. Post-streptococcal glomerulonephritis in Sydney: a 16-year retrospective review. J Paediatr Child Health 2007; 43:446.*

14. *Noris M, Remuzzi G. Hemolytic uremic syndrome. J Am Soc Nephrol 2005; 16:1035.*
15. *Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. Am J Kidney Dis 1997; 30:621.*
16. *Johnson RJ, Couser WG. Hepatitis B infection and renal disease: clinical, immunopathogenetic and therapeutic considerations. Kidney Int 1990; 37:663.*
17. *Rao TK, Filippone EJ, Nicastri AD, et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. N Engl J Med 1984; 310:669.*
18. *Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004; 15:241.*
19. *Niles JL, Böttinger EP, Saurina GR, et al. The syndrome of lung hemorrhage and nephritis is usually an ANCA-associated condition. Arch Intern Med 1996; 156:440.*
20. *Sinico RA, Radice A, Corace C, et al. Anti-glomerular basement membrane antibodies in the diagnosis of Goodpasture syndrome: a comparison of different assays. Nephrol Dial Transplant 2006; 21:397.*
21. *Lloyd W, Schur PH. Immune complexes, complement, and anti-DNA in exacerbations of systemic lupus erythematosus (SLE). Medicine (Baltimore) 1981; 60:208.*
22. *D'Amico G, Colasanti G, Ferrario F, Sinico RA. Renal involvement in essential mixed cryoglobulinemia. Kidney Int 1989; 35:1004.*
23. *Hebert LA, Cosio FG, Neff JC. Diagnostic significance of hypocomplementemia. Kidney Int 1991; 39:811.*
24. *Heaf J. The Danish Renal Biopsy Register. Kidney Int 2004; 66:895.*
25. *Braden GL, Mulhern JG, O'Shea MH, et al. Changing incidence of glomerular diseases in adults. Am J Kidney Dis 2000; 35:878.*
26. *Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int 1978; 13:159.*
27. *Leung N, Behrens J. Current approach to diagnosis and management of acute renal failure in myeloma patients. Adv Chronic Kidney Dis 2012; 19:297.*
28. *European Association for the Study of the Liver. Recommendations on treatment of hepatitis C. 2014 http://files.easl.eu/easl-recommendations-on-treatment-of-hepatitis-C.pdf (Accessed on April 14, 2014).*
29. *Vasculitis Stichting, Vormen van vasculitis, 2013. In: www.vasculitis.nl*
30. *Beck L.H. Jr, Bonegio R.G., Lambeau G., Beck D.M., Powell D.W., Cummins T.D., Klein J.B., Salant D.J.. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009; 361: 11-21.*
31. *Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. Am J Kidney Dis 1988; 11:449.*
32. *Baldwin DS, Neugarten J, Feiner HD, et al. The existence of a protracted course in crescentic glomerulonephritis. Kidney Int 1987; 31:790.*
33. *Whittier WL K.S.G.R.E., Rovin BH (Ed), Forman JP (Ed) Indications for and complications of renal biopsy. In: Waltham, MA: Wolters Kluwer; 2013;*
34. *Katopodis KP, Katsios CG, Koliousi EL, et al. Life-threatening hemorrhage from abdominal aorta following a percutaneous renal biopsy. Clin Nephrol 2006; 65:446.*
35. *Corapi KM, Chen JL, Balk EM, Gordon CE. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. Am J Kidney Dis 2012; 60:62.*
36. *Madaio MP. Renal biopsy. Kidney Int 1990; 38:529.*
37. *Clinical competence in percutaneous renal biopsy. Health and Public Policy Committee. American College of Physicians. Ann Intern Med 1988; 108:301.*
38. *Appel GB. Renal biopsy: How effective, what technique, and how safe. J Nephrol 1993; 6:4.*
39. *Gross JL, de Avezedo MJ, Silveiro SP. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care 2005 Jan;28(1):164-76.*

Prostate cancer screening in the Netherlands; not yet

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Summary

Background: Prostate cancer is the most common type of cancer in men in the Netherlands. From an age of 50 years old on there is a fast increase in incidence, prevalence and death due to prostate cancer. Thus, a screening program could lead to earlier diagnosis and reduced mortality. We assessed whether a prostate cancer screening program is indicated in the Netherlands.

Methods: A literature search has been conducted to find scientific proves and ethical arguments dealing with prostate cancer screening.

Results: Published data from two ongoing large randomized controlled trials showed conflicting results concerning mortality reduction due to screening. Observational studies also showed conflicting results. Screening has some limitations such as a high risk of overdiagnosis and overtreatment, low accuracy of PSA-test and high costs. Ethical arguments against screening are based on the principles of non-maleficence and patients autonomy.

Conclusion: A prostate cancer screening program is not yet indicated in the Netherlands. Results from ongoing large multicenter studies have to be awaited. Currently, screening can be conducted in individualized patients after informed decision making.

Introduction

Prostate cancer is the most common type of cancer in men in the Netherlands.[1] From an age of 50 years old on there is a fast increase in incidence, prevalence and death due to prostate cancer.[1] Prostate cancer is found in 45% of men who died due to other causes than prostate cancer.[2] The tumor often grows slowly, leading to a prostate cancer incidence of 1,2% in men older than 45 years old, while only accounting for 0,4% of the total mortality of those group men.[1]

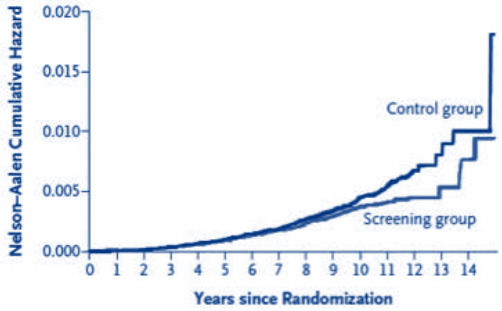
A combination of digital rectal examination (DRE) and PSA test form the initial diagnostic examination in patients in whom there is clinical suspicion for prostate cancer. Recently the PCA3 test has been introduced to determine whether re-biopsies are indicated.[3] Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is also found to be a useful modality for the precise detection and staging of early prostate cancer.[4]

Prostate cancer mortality is mainly related to the tumor stage and grade at the time of diagnosis. The five-year survival is 100% in patients with stage 1 prostate cancer and 61% in patients with stage 4 at time of diagnosis.[1] Thus, a screening program leading to earlier diagnosis could potentially reduce prostate cancer specific mortality. We assessed whether a prostate cancer screening program in the Netherlands is indicated in men aging 50-74 years old by looking at the currently available data on prostate cancer screening.

Medical-scientific considerations

The most important scientific consideration for screening is the effectiveness. The European Randomised study of Screening for Prostate Cancer (ERSPC) showed that prostate cancer screening reduced prostate cancer mortality by 21% after 9 years follow-up (figure 1).[5] Prostate cancer mortality reduction was comparable after 11 years and 13 years follow-up. [6,7] However, the study also found some potentially important side effects of prostate cancer screening. First, there is a high risk of overdiagnosis, which is estimated to be 40-50% of the cases detected by screening and which is much higher than overdiagnosis rates in other screening programs.[7,8] This often results in overtreatment with subsequent side effects. [9-11] However, a modeling study that was partly based on data from the ERSPC study showed that with a 4-year screening interval there was (despite the high rate of overdiagnosis and overtreatment) a gain of 52 life-years and a gain of 41 quality-of-life-adjusted life-years (QALYs) per 1000 men.[11]

Figure 1: Cumulative risk of death from prostate cancer



Second, a large group of 781 men would need to undergo a PSA test to prevent one death.[7] The PSA test, test results and related anxiety may negatively influence the quality of life of this large group of men. Third, 75.8% of the biopsies would be unnecessary and can cause complications.[7,12-14]

Another large randomized controlled trial that has been conducted in the United States showed no difference in mortality rates during a follow-up of 13 years between patients undergoing a combination of PSA test screening and DRE and controls.[15] However, an important limitation of this study was that more than half of the men randomized to the control arm were screened prior to the study.

Some observational studies showed that prostate cancer mortality rates declined with the introduction of a screening program.[16-18] However other studies found no 3 difference in mortality rates. Moreover one study showed that mortality rates declined over the years, independent of screening introduction.[19,20]

Furthermore the PSA-test is not accurate in detection prostate cancer.[21] A PSA-test with a cutoff value of 4ng/mL has a sensitivity of 21% and a specificity of 91% for detecting prostate cancer.[21] The low sensitivity will often give false-negative results and falsely reassure patients. The high percentage of false-positive results (70%) that can be caused by a benign prostate hypertrophy, prostatitis, drug use and recent ejaculation are also likely to cause a psychological burden that can last for one year after the PSA-test.[22-26]

Finally, prostate cancer screening will double the healthcare-costs of prostate cancer.[27] It is astounding that 39% of the total costs for screening is because of overdiagnosis.[27] Taking these studies together we see that the effectiveness of screening is not clear on reducing mortality rates and the harm benefit ratio is not yet optimal. Therefore, many committees have recommended against a population based screening program, but rather advised an individualized approach. [28-33] Screening can be conducted in individual cases with a life expectation of at least 10 years.[34] In high risk patients (positive family history or black race) screening can be conducted from an age of 45 years on and in normal risk patients from 50 to 75 years old.[35] Physicians should involve men in the decision whether to screen with the use of the PSA test and should give sufficient information about the risks and benefits of screening.

Ethical aspects

For prostate cancer screening there is ethically a consideration to be made between the ethical principles of non-maleficence and beneficence. The ethical principle of non-maleficence can be defined as “do not harm”, while the principle of beneficence can be defined as “do good”. There is a large group of men that will be harmed by screening, but there are also a few patients that will benefit from screening. From a perspective of utilitarianism one can argue that the well being of a large group is more important, then that of one person. Moreover, when considering a screening program one should concentrate on population results rather than individual results, therefore not harming the population is of greater value then doing good to only a few men.

This argument depends on the effectiveness of a screening program and is not specific for prostate cancer screening, but generally applies to screening programs. Therefore if the ongoing studies find a higher effectiveness of prostate cancer screening, then this ethical argument is to be reconsidered.

Furthermore, a screening program generally need to achieve a high attendance, therefore governments often promote it. Due to this promotion patients may think that it is a common thing to participate in the screening program and that it is something they should do as good citizens. Therefore this may partially abdicate their right of free choice and thus, is against the principle of autonomy.

This argument applies to all screening programs. In screening programs that showed to be effective this argument was no valid reason to stop introduction of the screening programs.

Conclusion

We assessed whether prostate cancer screening is indicated in the Netherlands. In our opinion (and not necessarily a widely supported urologists view) a prostate cancer screening program is not yet indicated, because of contradicting evidence on effectiveness of screening in reducing mortality, the high risk for overdiagnosis and overtreatment, the low accuracy of the PSA-test and the high costs. Ethical arguments against screening are based on the principles of non-maleficence and patients autonomy.

Almost all the arguments against prostate cancer screening result from the low performance characteristics of the PSA test. If the ongoing large multicenter studies find a higher effectiveness of prostate cancer screening after a longer follow-up or if the PSA test can be used in a more accurate way, for instance by combining it with digital rectal examination or by taking patient characteristics in consideration then a prostate cancer screening program is to be reconsidered.

Currently, screening can be conducted in individualized men, but physicians should involve men in the decision whether to screen with the use of the PSA test and should give sufficient information about the risks and benefits of screening.

References

1. *Integraal Kankercentrum Nederland Cijfers over kanker. In; 2012;*
2. *Sanchez-Chapado M., Olmedilla G., Cabeza M., et al. Prevalence of prostate cancer and prostatic intraepithelial neoplasia in Caucasian Mediterranean males: An autopsy study. Prostate. 2003; 54: 238-247.*
3. *Schroder F.H., Hugosson J., Roobol M.J., et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009; 360: 1320-1328.*
4. *Schroder F.H., Hugosson J., Roobol M.J., et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med. 2012; 366: 981-990.*
5. *Schroder F.H., Hugosson J., Roobol M.J., et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014:*

6. *Draisma G., Boer R., Otto S.J., et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 2003; 95: 868-878.*
7. *Cooperberg M.R., Lubeck D.P., Meng M.V., et al. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004; 22: 2141-2149.*
8. *Heijnsdijk E.A., Wever E.M., Auvinen A., et al. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med. 2012; 367: 595-605.*
9. *Hakama M.A., A. Cancer screening. In: Heggenhougen K, Quah SR, eds International encyclopedia of public health. San Diego, CA: Academic Press; 2008; 464-480.*
10. *Loeb S., Carter H.B., Berndt S.I., et al. Complications after prostate biopsy: data from SEER-Medicare. J Urol. 2011; 186: 1830-1834.*
11. *Nam R.K., Saskin R., Lee Y., et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. J Urol. 2010; 183: 963-968.*
12. *Wagenlehner F.M., van Oostrum E., Tenke P., et al. Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. European urology. 2013; 63: 521-527.*
13. *Andriole G.L., Crawford E.D., Grubb R.L., 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst. 2012; 104: 125-132.*
14. *Bartsch G., Horninger W., Klocker H., et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. Urology. 2001; 58: 417-424.*
15. *Roberts R.O., Bergstralh E.J., Katusic S.K., et al. Decline in prostate cancer mortality from 1980 to 1997, and an update on incidence trends in Olmsted County, Minnesota. J Urol. 1999; 161: 529-533.*
16. *Collin S.M., Martin R.M., Metcalfe C., et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. The Lancet Oncology. 2008; 9: 445-452.*
17. *Lu-Yao G., Albertsen P.C., Stanford J.L., et al. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. BMJ (Clinical research ed). 2002; 325: 740.*
18. *Oliver S.E., Gunnell D., Donovan J.L. Comparison of trends in prostate-cancer mortality in England and Wales and the USA. Lancet. 2000; 355: 1788-1789.*
19. *Wolf A.M., Wender R.C., Etzioni R.B., et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. 2010; 60: 70-98.*
20. *Catalona W.J., Richie J.P., Ahmann F.R., et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol. 1994; 151: 1283-1290.*
21. *Schroder F.H., van der Cruijsen-Koeter I., de Koning H.J., et al. Prostate cancer detection at low prostate specific antigen. J Urol. 2000; 163: 806-812.*
22. *Herschman J.D., Smith D.S., Catalona W.J. Effect of ejaculation on serum total and free prostate-specific antigen concentrations. Urology. 1997; 50: 239-243.*
23. *Simardi L.H., Tobias-MacHado M., Kappaz G.T., et al. Influence of asymptomatic histologic prostatitis on serum prostate-specific antigen: a prospective study. Urology. 2004; 64: 1098-1101.*
24. *Lin K., Lipsitz R., Miller T., et al. Benefits and harms of prostate-specific antigen screening for prostate cancer: an evidence update for the U.S. Preventive Services Task Force. Ann Intern Med. 2008; 149: 192-199.*
25. *Heijnsdijk E.A., der Kinderen A., Wever E.M., et al. Overdetection, overtreatment and costs in prostate-specific antigen screening for prostate cancer. Br J Cancer. 2009; 101: 1833-1838.*
26. *Moyer V.A., Force U.S.P.S.T. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012; 157: 120-134.*
27. *Horwich A., Hugosson J., de Reijke T., et al. Prostate cancer: ESMO Consensus Conference Guidelines 2012. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013; 24: 1141-1162.*
28. *Qaseem A., Barry M.J., Denberg T.D., et al. Screening for prostate cancer: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2013; 158: 761-769.*
29. *The Canadian Task Force on Preventive Health Care In; 2006;*
30. *The United Kingdom National Screening Committee In; 2010;*
31. *The Australian Cancer Council In; 2011;*

Smoking cessation as primary therapy for smokers with an erectile dysfunction

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Introduction

Despite many campaigns conducted over the last years, smoking still remains a major health issue worldwide. The same applies to the current situation in the Netherlands; 26% of the Dutch population older than 15 years is a smoker.[1] A shocking number, especially given the known consequences. Unfortunately, informing about cardiovascular diseases and cancer does not threaten the smoker anymore, given the fact that the prevalence of smoking does not decrease any further. A new campaign measure is needed. Therefore, at the beginning of this century, Tengs et al the significant risk of erectile dysfunction pointed at (ED) among smokers.[2] The high prevalence of ED can be an effective way to alarm smokers again.

An erectile dysfunction is defined as a continuous or recurrent inability to achieve or maintain an erection sufficient for sexual activity over a period of at least 6 months.[3] Almost 17% of the Dutch male population older than 18 years. In 2004 matched the criteria for ED, highlighting the impact of this frequent quality of life and limiting complaint.[4] Currently, oral phosphodiesterase type 5 (PDE-5) inhibitors are considered first line therapy for males presenting with ED as a result of a physical problem, e.g. neurological or vascular disorders.[3,5] Even in case of non-physical, psychological disturbances, this medication is indicated for short-term support.[6]

However, the etiology of ED is multifactorial. Besides disease related problems. Next to pure pathological factors, lifestyle factors such as smoking, obesity and lack of physical contribute substantially. Multiple studies underpin the direct and independent risk of smoking, for it causes damage to the arteries and the vascular smooth muscle in general. As a result, the vascular resistance is increased and the smooth muscle cannot sufficiently relax, potentially leading to erectile dysfunction.[7,8] This has been scientifically proven many times.[2,9] To exemplify the impact, current research showed an increased risk of ED by 51% for current smokers en 20% for ex-smokers, as compared with never-smokers.[10]

Currently, guidelines indicate treatment with PDE-5 inhibitors as first line therapy. In the Netherlands, if prescribed by a physician, PDE-5 inhibitors are reimbursed by the insurer. Not in case of basic health insurance, but it is reimbursed in case of an additional insurance.[11] Regarding the lifestyle factors contributing to the etiology of ED, the question rises if first line therapy should primarily remain pharmalogical. Although, because of the limited reimbursement, PDE-5 inhibitors are less frequently prescribed than expect regarding the prevalence of ED, it still remains questionable. The distinction between taking responsibility for one's lifestyle and reimbursement of treatments, as solutions for health problems, becomes fuzzy. Should one citizen have to bear for the bad habits of one another?[12] Should we not tackle the lifestyle problems initially and ascertain the effectiveness of this intervention, before stepping up to pharmacological treatment? I believe that smokers who suffer from erectile dysfunction, have to quit smoking prior to receiving reimbursement of PDE-5 inhibitors.

Lifestyle intervention as an effective therapy

First, several studies emphasize that smoking cessation is an effective measure in ED treatment.[13-15] On top of the general knowledge that smoking comes along with an increased risk of coronary heart disease, the consequences for developing ED are well known too.[2] Even more, a therapy aimed at the reduction of cardiovascular risk factors significantly improved ED as well. It even improved in men who did not respond to treatment with PDE-5 inhibitors in the first place.[16] This brings the discussion if is it wise to start directly with medication, if a lifestyle intervention offers at least as effective results. After all, PDE-5 inhibitors are only effective in 40-80% of the cases.[7]

Results show that smoking cessation improves ED after six months in 25,7% more of the quitters than the non-quitters.[14] Furthermore, another study even reported an ED remission rate of 75% for successful quitters.[13] Improvement of ED (i.e. increased tumescence and quickly reached maximum excitement) provides more satisfaction, confidence and happiness.[4] Participants who fell back into old smoking habits, presented with three times more ED as compared to the consistent quitters.[13] On top of these long term effects, the short-term effects (i.e. 24-36 hr. after cessation) show significant improvement as well![17] In other words, the achievable result of smoking cessation is considerably, both of short and long term.

Next to the increased risk of ED for current smokers compared to ex-smokers and quitters to non-quitters[10], there is also a significant correlation between the number of pack years and the severity of ED; a more severe ED at the beginning of the treatment gives lower chances of improvement.[15] Taking this into account, would it not be contradictory to keep first line therapy pharmacologically?

The PDE-5 inhibitors effectuate an erection, but the ED will still continue to decline by continuation of smoking. By smoking cessation, the damage will not increase further and ED will improve. When this turns out not to be as effective as desired, PDE-5 inhibitors can still be considered additionally. Thanks to the already improved ED status, the medication will then be even more effective. Summarized, smoking cessation should definitely be integrated in the treatment of patients who both smoke as well suffer from ED.[14]

No need for unnecessary side-effects

Secondly, smoking cessation is a safer and less invasive remedy to treat ED. Of course smoking cessation is not an easy road. Professional support is necessary. Currently, there are a lot of possibilities for this support.[18] Even though it is extremely hard to stop smoking, it is still the better option over medication treatment. Pharmacological therapy, the current first line treatment, always comes with risks and side effects.[3] The most common side-effects are headache, flushing, dyspepsia (indigestion) and visual disturbances. In addition, diarrhea, dizziness and blushing frequently appear. Furthermore, these side-effects seem to be dose-related. The latter is alarming, since dosage increase is guided by effectiveness, causing an increasing risk if a certain dosage is considered inadequate.[5,7,19]

Two out of five studies in a meta-analysis reported complaints of headache and flushing.[5] Headache is a serious, very disturbing complaint for which patients frequently visit their doctor and this side-effect occurs in more than 10% of the users of PDE-5 inhibitors.[7,20]

Another additional difficulty, is the fact that the majority of ED patients is older than 40 years. There is a significant positive relationship between age, ED and various somatic disorders, such as diabetes mellitus and cardiovascular disease. Unfortunately, diabetic patients have an increased 3-7% risk of cardiovascular diseases such as ECG abnormalities, chest pain, heart failure, hypertension and varicosis on top of the regular common side-effects. Patients with hypertension have an additional increased risk of stroke, pulmonary edema and atrial fibrillation.[4,19]

The current policy of drugs as first line therapy creates new health issues, which leads to a conflict with one of the medical ethical principles: primum non nocere. Some of these side effects are so severe that it is highly questionable whether they outweigh the benefits of PDE-5 inhibitors. Although smoking cessation is also a physical and psychological burden, it has no long-term negative aspects. Therefore, it is preferred to first focus at the smoking before writing a recipe.

The financial benefit

Finally, smoking cessation is a cheaper remedy. Currently, Sildenafil (Viagra) is the most prescribed drug for ED treatment. The use of it has a strongly increasing prevalence in the Western world.[21] Although since 2013 the patent for Viagra has fallen, the prices for medication are still about €4 a pill.[22] Though there has been no cost-effectiveness study published in the Netherlands so far, other countries teach us that the economic burden of ED is substantial and the head of this expenditure is formed by – not surprisingly – pharmacotherapy.[21] Apart from the pharmacotherapeutical costs, the aforementioned new health issues bring also additional costs with them, including time of the physician, research and therapy.

As an illustration, somebody who smokes a pack of cigarettes a day already himself pays €2184 a year (€6 x 7 days x 52 weeks). A consult at an urologist costs about €120 and the costs of Sildenafil can rise till over €200 when weekly used, which both will be paid out of health insurance. All in all, smoking is a major burden on health care, while stamina, potency and a good life expectancy are priceless.

Of course, one could argue that smoking cessation also burdens the society costs. With the aim of protecting public health, smoking cessation programs are reimbursed by health insurance companies. This is certainly true, but the costs will definitely be lower eventually. The program is financed once and will then yield benefits for many years.[23] Both the saved costs of the PDE-5 inhibitors as the prevented new health issues, make that smoking cessation is a cheap remedy for ED.

An ethical perspective

Another objection could be introduced from an ethical perspective. For years, people have been arguing about the reimbursement of pharmacotherapeutics in the treatment of ED. Opponents state that every Dutch citizen has a right to equal treatment.[24] Another relevant ethical argument comes from solidarity, which implies that people with an unequal health risk, still equally pay for health care. However, this is refuted by fault reasoning, emphasizing self-interest and responsibility in particular, which makes solidarity not infinite. Smoking is an addiction and can be seen as a disease itself. Quitting is hard, but in the end the patient decides to smoke for his or herself. The autonomy of the patient should certainly remain unharmed in my opinion, but that does not mean that he or she can shove the responsibility onto someone else. One does not need to pay for someone else's unhealthy lifestyle. When a problem can possibly be solved by a lifestyle intervention, that's the preferred option.[25]

Because of the current economic situation, major cuts are being made in health care and (additional) insurances are critically reviewed at the moment. The reimbursed amount will be charged on the insurance premium. Is it fair that those who take the responsibility for their own health's sake, indirectly have to pay for the health costs of smokers?

Conclusion

In conclusion, smoking cessation would be a better first line therapy than PDE-5 inhibitors, regarding smokers with ED. It is a more effective, safer and cheaper remedy. After all, PDE-5 inhibitors are not always effective[7] and a substantial amount of studies have shown that smoking cessation has been proven to be an effective method to reduce ED symptoms. Moreover, the use of PDE-5 inhibitors will be less effective if the patient keeps smoking, due to increasing damage.[4,10,13-16] The multiple side effects of PDE-5 inhibitors are in contrary with the principle 'primum non nocere'.[4,5,7,19] Derived from foreign studies, high costs are ineluctable given the pharmacological treatment and associated health problems.[21] The assumption that the costs of smoking cessation are higher is unjustified[23] and no ethical principles are at stake.[24,25] Of course it is also important to keep in mind that smoking is an addiction and that it is very hard to quit. However, there are a lot of options for professional support nowadays. Together with the generally increased health it is certainly worth to try quitting.

In short, smoking men with ED should first quit smoking before getting reimbursed PDE-5 inhibitors. Smoking cessation is more effective, safer and cheaper and should therefore be considered first line therapy.

References:

1. *Trimbos Instituut. Hoeveel mensen roken? Available at: http://www.rokeninfo.nl/publiek/cijfers/hoeveel-mensen-roken.*
2. *Tengs T.O., Osgood N.D. The link between smoking and impotence: two decades of evidence. Prev Med. 2001; 32: 447-452.*
3. *Leusink P., De Boer L.J., Vliet Vlieland C.W., et al. NHG-Standaard Erectiele disfunctie. Huisarts Wet. 2008; 51: 381-394.*
4. *de Boer B.J., Bots M.L., Lycklama a Nijeholt A.A., et al. Erectile dysfunction in primary care: prevalence and patient characteristics. The ENIGMA study. Int J Impot Res. 2004; 16: 358-364.*
5. *Ding H., Du W., Wang H., et al. Efficacy and safety of udenafil for ile dysfunction: a meta-analysis of randomized controlled trials. Urology. 2012; 80: 134-139.*
6. *van Lankveld J.J., van den Hout M.A., Spigt M.G., et al. Cognitive changes predict continued recovery of erectile functioning versus relapse after discontinuation of sildenafil treatment for male erectile dysfunction. Psychosom Med. 2003; 65: 709-718.*
7. *Bangma C.H. 2008 Erectiele dysfunctie. In: Urologie. Houten: Bohn Stafleu van Loghum;2008; 111-119.*
8. *de Jongh T.O.H., de Vries H. 2011 Erectiele dysfunctie. In: Diagnostiek van alledaagse klachten: bouwstenen voor rationeel probleemoplossen. Houten: Bohn Stafleu van Loghum;2011; 465-472.*
9. *Selvin E., Burnett A.L., Platz E.A. Prevalence and risk factors for erectile dysfunction in the US. Am J Med. 2007; 120: 151-157.*
10. *Cao S., Yin X., Wang Y., et al. Smoking and risk of erectile dysfunction: systematic review of observational studies with meta-analysis. PLoS One. 2013; 8: e60443.*
11. *ZorgverzekeringWijzer. Vergoeding erectiepillen 2014. Available at: http://www.zorgverzekeringwijzer.nl/zorgvergoedingen/Erectiepillen.*
12. *Polinski J.M., Kesselheim A.S. Where cost, medical necessity, and morality meet: should US government insurance programs pay for erectile dysfunction drugs? Clin Pharmacol Ther. 2011; 89: 17-19.*
13. *Harte C.B., Meston C.M. Association between smoking cessation and sexual health in men. BJU Int. 2012; 109: 888-896.*
14. *Chan S.S., Leung D.Y., Abdullah A.S., et al. Smoking-cessation and adherence intervention among Chinese patients with erectile dysfunction. Am J Prev Med. 2010; 39: 251-258.*
15. *Pourmand G., Alidaee M.R., Rasuli S., et al. Do cigarette smokers with erectile dysfunction benefit from stopping?: a prospective study. BJU Int. 2004; 94: 1310-1313.*
16. *Gupta B.P., Murad M.H., Clifton M.M., et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2011; 171: 1797-1803.*
17. *Sighinolfi M.C., Mofferdin A., De Stefani S., et al. Immediate improvement in penile hemodynamics after cessation of smoking: previous results. Urology. 2007; 69: 163-165.*
18. *Trombus Instituut. Begeleiding. Available at: http://www.rokeninfo.nl/publiek/info-over-stoppen/hulp-bij-stoppen/begeleiding.*
19. *Tsertsvadze A., Yazdi F., Fink H.A., et al. Oral sildenafil citrate (viagra) for erectile dysfunction: a systematic review and meta-analysis of harms. Urology. 2009; 74: 831-836.*
20. *Van der Linden M.W., Westert G.P., Bakker D.D., et al. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk: klachten en aandoeningen in de bevolking en in de huisartspraktijk. 2004:*
21. *Wessells H., Joyce G.F., Wise M., et al. Erectile dysfunction. J Urol. 2007; 177: 1675-1681.*
22. *Stichting Farmaceutische Kengetallen. Succesvolle introductie generiek Viagra. Available at: http://www.sfk.nl/nieuws-publicaties/PW/2013/succesvolle-introductie-generiek-viagra.*
23. *Trombus Instituut. Vergoeding Stoppen met roken in 2014. Available at: http://www.rokeninfo.nl/publiek/vergoedingen.*
24. *Stolk E.A., Brouwer W.B.F., Busschbach J.J.V. Vergoeding van Viagra stuit op waarden en normen. Medisch Contact. 2000; 17: 626-629.*
25. *de Beaufort I. 2008 Wie zijn billen brandt... moet zelf de rekening betalen? In: De Kwestie: praktijkboek ethiek voor de gezondheidszorg. Den Haag: LEMMA;2008; 180-186.*

Liquid poison for children, for sale in every supermarket

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Introduction

In today's society, fatigue and a temporary cognitive malfunction caused by sleep deprivation are not rare phenomena. It is estimated that the amount of adults that sleeps less than 6 hours a night has increased dramatically over the past 20 years.[1] Research shows that the majority of adolescents does not get the recommended amount of sleep, which results in sleepiness during the day.[2] The most common cause of sleepiness in adolescents is a lack of sleep, which is the consequence of an interaction between puberty and academic, social and curricular demands. Research shows that 45.7% of adolescents is sleepy during the day at least once a week.[2] One may doubt the severity of this. After all, isn't everybody sleepy sometimes? Research has shown that sleepiness can effect academic functioning, psychological functioning and behavior.[2] Furthermore, sleep deprivation is mentioned as a factor in many accidents in both transport and industry.[3] hence, it really is alarming that sleepiness is such a common phenomenon.

Today's youth has found a way to combat this increasing shortage of alertness: Energy drink. An energy drink can be defined as a drink containing ingredients to boost the drinker's energy. This drink helps youngsters to stay mentally alert. It also improves their physical performance, for example in sports. It is suggested that energy drinks increase the running distance that is travelled during team sports with 7-9%.[4] In 2013, Wesnes et al investigated whether energy shots have an effect on cognitive functioning and the mood of healthy volunteers. They showed positive effects, caused by energy shots, on cognitive functioning and mood in partially sleep deprived volunteers. After receiving the energy shot, volunteers were able to maintain their initial attention level for a period of 6 hours, while the performance of the placebo group decreased over time. They found that energy shots help to preserve attention, concentration, the processing of information and the vigilance over a 6 hour period. Also, they found a positive effect on both the short and the long term memory.[5] This overview shows that energy shots can help to improve performance in all sorts of daily tasks in partially sleep deprived volunteers.[5] So, energy drink appears to be a panacea against fatigue, but is that really the case? Unfortunately, this medium also has a downside. Energy drinks contain, among other ingredients, large amounts of caffeine. Caffeine consumption by adolescents is related to addiction, bad sleep and feasible developmental problems. In addition, the consumption of large amounts of energy drinks can lead to severe health problems.[6-14]

Now, the question arises whether it is responsible that it is possible for our youngsters to buy energy drink without constraints, considering the possible harmful effects. But is energy drink truly that dangerous? And how often do these harmful effects actually occur? In fact, aren't our youngsters old enough to decide for themselves whether or not they want to take such risks? The major question is whether our government should forbid the sale of energy drinks to youngsters.

Medical and toxicological aspects

To answer this question, the adverse effects of energy drinks must be accurately examined. Also, it must be investigated in which way youngsters use energy drinks and to what extent they do so.

Ingredients

The main ingredient of energy drinks is caffeine. Caffeine's toxic threshold is known to be at 400 mg/day for healthy adults (≥19 years), 100 mg/day for healthy adolescents (12-18 years) and 2.5 mg/kg/day for healthy children (<12 years). A can of energy drink that weights around 28 grams contains 77 mg caffeine (or 1.1 mg/kg for a man weighing 70 kg and twice as much, 2.2 mg/kg, for a 35 kg weighing teenager). This shows that adolescents almost reach their daily intake maximum after one can of energy drink, as a result of which caffeine intoxication is lurking.[12] Caffeine intoxication is a clinical syndrome that is characterized by anxiety, irritability, stress, insomnia, tremor, tachycardia and palpitations.[12] Other important ingredients that energy drinks contain are Guarana extract, Taurine, Ginseng and sugar.[7] Guarana is the world's most caffeine containing plant and is used to add extra caffeine to energy drinks.[14] Studies suggest that the amount of caffeine that Guarana contains (40-80 mg/gram) is not always reported on the packaging and should therefore be added to the amount of caffeine reported on a can.[7] This would mean that adolescents already reach their maximum daily intake of caffeine after one can of energy drink and are therefore at considerable risk for caffeine intoxication.[6] Taurine is an amino-acid that is thought to magnify the effect of caffeine. A normal diet accounts for 20-200 mg Taurine, while the amount of Taurine in energy drinks varies from 600 to 1000 mg per can.[10] Although hard evidence proving the adverse effects of such amounts of Taurine is lacking, there are suspicions and many countries have either limited or prohibited the sale of Taurine containing energy drinks.[10]

Ginseng is a substance that has, among other things, positive effects on stamina. Ginseng's therapeutic doses is 100-200 mg/day, while energy drinks contain 0-100 mg.[10] Some negative effects that can be caused by Ginseng are insomnia, vaginal bleedings, tachycardia, palpitations, hypertension, edema, headache and vertigo.[10] The sugar concentration in energy drinks exceeds the recommended maximum daily amount with 2 or 3 times. It is known that excessive sugar intake can lead to dental erosion, diabetes and obesities.[10] Furthermore, heavy energy drink consumption can result in liver- and nerve damage caused by the excessive consumption of vitamin B by which it is accompanied. While high vitamin B intake is not necessarily malicious and can in fact be beneficial, there are serious concerns about the presence of large amounts of vitamin B, especially vitamin B6, in many energy drinks.[14] Table 1 shows the main ingredients of energy drinks and their adverse effects.

Usage

Although energy drinks are being used by all age groups, it are mainly youngsters that use it on a large scale. Children (<12 years), adolescents (12-18 years) and young adults (19-25 years) account for half of the market for energy drinks.[11] In 2013, Seifert et al showed that the majority of deliberate encounters with energy drinks can be ascribed to teenagers, while children's (<6 years) contact with energy drinks is mostly unintentional.[12] Is this excessive use of energy drinks reflected in social problems? Unfortunately, it is. In the US, there has been a tenfold increase in first aid visits due to energy drink intake between 2005 and 2009 (from 1128 to 13114) and these numbers are still rising substantially (20783 in 2011).[12] Apart from the effect on physical health, energy drinks also influence psychological well-being in a stronger way than for example coffee does. In 2013, Jackson et al showed that energy drink users are more likely to run into trouble at home, in school and on work compared to users of beverages that only contain caffeine.[8] Although people normally drink energy drink from a can, it is also often used in combination with other drinks. The most popular drinks to combine with energy drinks are alcohol and other caffeine containing products.[7] The usage of the combination of alcohol and energy drinks, called AMEDS, is not without risk. It has been a long tradition to get somebody sober by administering large amounts of coffee to a person. This makes the person believe that the intoxication has become less, while the physical impairments are not really reduced.[13] AMEDS have more or less this effect. They reduce the subjective perception of intoxication, but do not improve the objective skills such as motor coordination or reaction time compared to the use of alcohol alone.[7] An AMED user will feel less drunk than an alcohol user, but this is physically not the case. This can lead to risky behavior because AMED users overestimate their own capabilities.[9]

Regulation

The energy drink industry advertises a lot, emphasizing the positive effects that energy drinks have on energy and alertness. These companies focus on athletes, students and people who have professions that require a lasting alertness.[7] Australian research showed that in 2009, the energy drink industry spent almost 15 million AUD on marketing in Australia alone.[8] Partly through this, these companies have achieved that energy drinks are not considered harmful, while they should be. Before 2011, American stores even sold prepacked AMEDS. Due to safety concerns, the FDA (Food and Drug Administration) withdrew these drinks from the market.[12]

Table 1 - Main ingredients of energy drinks and their adverse effects.[10]

Main ingredients	Adverse effects
Caffeine	Nausea, heart palpitations, ventricular and atrial tachycardias, headache, insomnia, anxiety, irritability, seizure, hallucinations, hypokalemia, rhabdomyolysis
Guarana	Insomnia, nervousness, restlessness, tachycardia, tremors, anxiety, chest pain, dysrhythmias
Taurine	Insufficient evidence to prove adverse effects
Sugar	Dental erosions, cavities, diabetes, obesity
Ginseng	Insomnia, breast tenderness, vaginal bleedings, amenorrhea, tachycardia, heart palpitations, hypertension, edema, headaches, vertigo, euphoria, mania

Ethical consideration

Mainly because of the health effects discussed above, the discussion around energy drinks is thriving in the Netherlands. Some plead for a prohibition of the sale of energy drinks to youngsters. The question then arises as to whether such a prohibition can be ethically justified. The most frequently mentioned argument in favor of a prohibition is of course the fact that energy drink use can give rise to severe health risks, according to studies.[6-14] In accordance with the 'do-no-harm principle', it is considered irresponsible to expose people to such risks. Also, it is reported that children, adolescents and young adults account for half of the market for energy drinks. While children are not completely mentally incompetent and the big companies do not literally force them to drink energy drinks, the advertising strategies that specifically focus on children can be called misleading, since they only light out the positive sides of energy drink use. These marketing strategies can limit the children's possibility to make an autonomous choice, making these children incapable of what is called 'autonomous self-determination'. Research has shown that the immaturity of children's brains, in particular the frontal lobes, hampers their ability to make well-considered decisions.[16] Because children are still susceptible for this sort of advertisement, they should be protected by their government. In fact, it is highly remarkable that such a prohibition does not currently exist. The sale of tobacco and alcohol to children has been prohibited for a long time. How can we justify that this product, that has scientifically proved to be harmful for youngsters, is so easily obtainable? Critics underline that scientific studies proved that energy drinks have positive cognitive and physical effects and that they should therefore be freely obtainable.[5, 15] They call on the 'justice principle' and pose that children who use energy drinks responsible, will be victimized by the abusers through such a prohibition. While it is not deniable that energy drinks have some short term positive effects, that is no reason not to prohibit it. Cocaine also has short term positive effects, but it is banned because the disadvantages overbalance the advantages on the short term.

This is also the case with energy drinks. In addition, it can be stated that responsible use of energy drinks equals no use, given the toxicity that is already present in small amounts.[12] Children's autonomy is often mentioned as an argument to not prohibit energy drinks. As said, it is my opinion that children are so easily influenced by marketing strategies carried out by big companies, their environment and other factors that they are incapable of making an independent autonomous decision concerning the use of energy drink. Because they are unable to fully oversee the consequences, they should be protected by the government. Some people wonder what else will be prohibited once we start banning energy drinks. After all, cola is also harmful. Apart from the fact that this is a so called 'inclined slope fallacy', energy drinks contain a unique combination of harmful substances that other soft drinks do not contain.[6, 7, 10, 12] Therefore, the comparison with cola falls short. Also, it has been shown that the use of energy drink leads to more social problemacy than the use of other drinks that only contain caffeine.[8]

Conclusion

The Dutch government should prohibit the sale of energy drinks to youngsters. Apart from the fact that energy drinks are very harmful, children are not yet capable of making an autonomous decision concerning the use of energy drinks and they should therefore be protected by the government. A similar legislation as currently exists for tobacco and alcohol would be appropriate. A prohibition for adults is not required, since they can oversee the consequences of energy drink use and are less susceptible to marketing strategies carried out by big companies. These regulations should be applied under the condition that a warning regarding the possible adverse health effects must be placed on the packaging to make sure that adults that choose to use energy drinks, do so well informed.

References:

1. *Palma J.A., Urrestarazu E., Iriarte J. Sleep loss as risk factor for neurologic disorders: a review. Sleep Med. 2013; 14:229-36.*
2. *Moore M., Meltzer L.J. The sleepy adolescent: causes and consequences of sleepiness in teens. Paediatr Respir Rev. 2008; 9:114-20.*
3. *Jackson M.L., Gunzelmann G., Whitney P. et al. Deconstructing and reconstructing cognitive performance in sleep deprivation. Sleep Med Rev. 2013; 17:215-25.*
4. *Del Coso J., Portillo J., Munoz G. et al. Caffeine-containing energy drink improves sprint performance during an international rugby sevens competition. Amino Acids. 2013; 44:1511-9.*
5. *Wesnes K.A., Barrett M.L., Udani J.K. An evaluation of the cognitive and mood effects of an energy shot over a 6h period in volunteers: a randomized, double-blind, placebo controlled, cross-over study. Appetite. 2013; 67:105-13.*
6. *Clauson K.A., Shields K.M., McQueen C.E. et al. Safety issues associated with commercially available energy drinks. J Am Pharm Assoc (2003). 2008; 48:e55-63.*
7. *Gunja N., Brown J.A. Energy drinks: health risks and toxicity. Med J Aust. 2012; 196:46-9.*
8. *Jackson D.A., Cotter B.V., Merchant R.C. et al. Behavioral and physiologic adverse effects in adolescent and young adult emergency department patients reporting use of energy drinks and caffeine. Clin Toxicol (Phila). 2013; 51:557-65.*
9. *Peacock A., Bruno R., Martin F.H. The impact of alcohol and energy drink consumption on intoxication and risk-taking behavior. Alcohol Clin Exp Res. 2013; 37:1234-42.*
10. *Rath M. Energy drinks: what is all the hype? The dangers of energy drink consumption. J Am Acad Nurse Pract. 2012; 24:70-6.*
11. *Seifert S.M., Schaechter J.L., Hershorin E.R. Health effects of energy drinks on children, adolescents, and young adults. Pediatrics. 2011; 127:511-28.*
12. *Seifert S.M., Seifert S.A., Schaechter J.L. et al. An analysis of energy-drink toxicity in the National Poison Data System. Clin Toxicol (Phila). 2013; 51:566-74.*
13. *Weldy D.L. Risks of alcoholic energy drinks for youth. J Am Board Fam Med. 2010; 23:555-8.*
14. *Wolk B.J, Ganetsky M., Babu K.M. Toxicity of energy drinks. Curr Opin Pediatr. 2012; 24:243-51.*
15. *Del Coso J, Ramirez JA, Munoz G, Portillo J, Gonzalez-Millan C, Munoz V, et al. Caffeine-containing energy drink improves physical performance of elite rugby players during a simulated match. Appl Physiol Nutr Metab. 2013; 38:368-74.*
16. *Schiebener J., Garcia-Arias M., Garcia-Vallamisar D. et al. Developmental changes in decision making under risk: The role of executive functions and reasoning abilities in 8- to 19-year-old decision makers. Child Neuropsychol. 2014; 16:1-20.*

Cerebellar infarction requires quick diagnosis and immediate treatment with intravenous thrombolytics. *A case report*

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Case report

A 61-year-old woman presented at the Emergency Department with acute vertigo, headache, nausea, vomiting and dysarthria. The patient was known for type 2 diabetes mellitus, hypercholesterolemia, hypothyroidism and hypertension. She used antihypertensive drugs, lipid-lowering drugs, thyroid hormone suppletion and oral antidiabetic drugs.

On examination she had a bidirectional gaze-evoked 1st degree nystagmus. There was diminished left-sided facial sensation, a right-sided facial palsy with peripheral features, a right-sided Horner's syndrome, limb ataxia on the right side and diminished sensation to pinprick in the left-sided limbs.

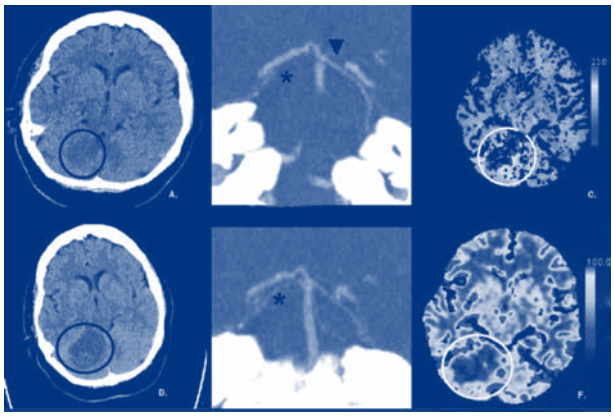

Figure 1: Acute phase scan. A. The ill-demarcated hypodense area in the vascular territory of the right SCA. B. MIP (maximum intensity projection) images showed only a posterior cerebral artery (PCA), but no right superior cerebral artery (SCA) (Black arrowhead: left SCA, Star: no right SCA) C. TTP (time to peak) perfusion imaging showed an area with a delayed time to peak (circled grey area): the penumbra.

Subacute phase scan (after 53 hours). D. The ill-demarcated area becomes well demarcated. E. Recanalization of the right SCA (Black star). F. CBV (cerebral blood volume) perfusion imaging showed an area (circled dark grey) with a decreased contrast: the ischemic core. Note that perfusion CT images (C, F) are usually displayed in color. For technical reasons grey-tones are used.

Diagnostic evaluation

Unenhanced cerebral computed tomography (CT) showed no signs of ischemia or haemorrhage (Figure 1). As shown in Figure 1B, CT angiography (CT-A) showed an occluded right superior cerebellar artery (SCA). A few calcifications of the aortic arch were noted, but additional CTA showed normal brachiocephalic arteries and no stenoses in both vertebral arteries. CT perfusion (CT-P, Figure 1C) showed a perfusion defect in the upper part of the right cerebellar hemisphere and extending into the right dorsal side of the pons, which corresponded to the vascular territory of the right SCA. An electrocardiogram (ECG) revealed no abnormalities. Two days after the first scan, CT-A showed recanalization of a very small right SCA and the CT perfusion confirmed ischemia of the vascular territory of the SCA (Figure 1E and 1F).

Treatment and outcome

The patient received treatment with intravenous alteplase directly after the unenhanced CT was performed. The door to needle time was 26 minutes. The patient was admitted to the stroke unit and a platelet inhibitor (clopidogrel) was started after several hours. During several days on our ward the patient's vertigo and nausea improved. She made a close to complete recovery of the right hemi-ataxia.

Risk factors for cardiovascular diseases were evaluated. We intensified secondary stroke prevention by increasing antihypertensive medication. Other risk factors like diabetes and dyslipidaemia were already well controlled with medication. No direct cause of the infarction, either atherothrombotic or cardiogenic, was found.

Discussion

Cerebellar infarcts account for 1.5% to 3% of ischaemic strokes. [1,2] The clinical presentation is diverse and highly variable; the main symptoms are vertigo, nausea and vomiting, gait instability and headache.[2] Lesions of the cerebellar hemispheres cause varying degrees of ataxia.

Most of these symptoms are often caused by common and benign disorders, which may explain the frequent misdiagnosis and delay in treatment.[2]

As shown in Figure 2 blood flow in the cerebellum is supplied mainly by three arteries: the posterior inferior cerebellar artery (PICA), which branches from the vertebral artery, the anterior inferior cerebellar artery (AICA) and superior cerebellar artery (SCA), both of which branch from the basilar artery.[3] The PICA provides the postero-inferior part, the AICA distributes to the antero-inferior part, and the SCA distributes to the superior part.[3]

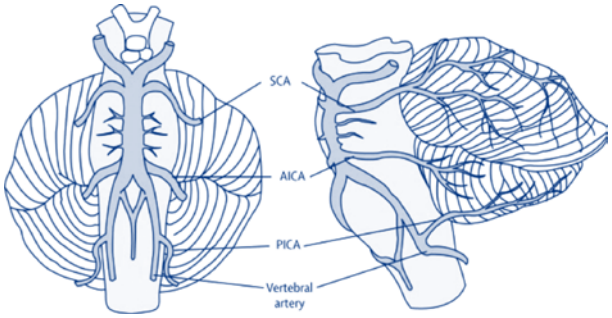

Figure 2. Arterial vascularization of brainstem and cerebellum.[2]

Proximal branches of the three main cerebellar arteries typically supply the lateral part of the brainstem; therefore coincident brainstem signs can be found in patients with cerebellar stroke.[2] So called "crossed" signs like ipsilesional cranial nerve and contralesional long tract signs suggest involvement of the brainstem.[2] Our patient presented with an ipsilesional right-sided facial palsy together with a diminished sensation of the left-sided face and left-sided limbs, both contralesional, suggesting brainstem involvement at the level of the pons.

Unenhanced CT rarely identifies early-stage cerebellar infarction, but is used to rule out intra-cerebral haemorrhage. Accurate neurological examination is crucial to identify cerebellar stroke.[2] Recognizing a cerebellar infarction is very important for quick treatment with thrombolytic agents and preventing potentially fatal complications, such as brainstem compression and obstructive hydrocephalus.[2]
CTA is important to identify the occluded vessel. CT-P is required to visualize the ischemic region and to determine the presence of potentially treatable penumbra.

When the clinical diagnosis of acute cerebral infarction is made, and unenhanced CT rules out intra-cerebral haemorrhage, prompt treatment with intravenous recombinant tissue plasminogen activator (iv rt-PA (alteplase)) within 4.5 hours of the onset of symptoms needs to be established unless there are contraindications.[4,5] The aim of treatment with intravenous rt-PA is to recanalize the occluded artery by lysis of the obstructing clot, which should lead to restored perfusion of brain tissue in the affected area. Intravenous thrombolysis has shown to be effective in improving outcome [4,6] The sooner that rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 minutes after onset.[4,5] In our patient early intravenous thrombolysis has led to complete recovery, although an infarct remained visible on repeat CT scanning.

An antiplatelet agent like clopidogrel is started after a delay of several hours after treatment with alteplase, because immediate treatment with antiplatelet agents has been associated with the occurrence of intracrebral hemorrhage. Identification and treatment of the underlying cardiovascular and cerebrovascular pathology will be done in the next 48 hours to prevent additional ischemia.[2] Most cerebellar infarcts do have a benign outcome.[7] Prognosis is poorer when the brainstem is also affected.[1]

Other or additional options for treatment are intra-arterial thrombolysis or mechanical thrombectomy. These treatments are still considered experimental, and their indication depends on the presence of a relevant arterial occlusion and on contraindications for intravenous thrombolysis like increased bleeding risk or elapsed time since first symptoms.[8,11]

Conclusion

This case illustrates that a cerebellar infarction often presents with common and non-specific symptoms. Basic knowledge of the symptoms of brainstem and cerebellar infarction is essential for an early and accurate diagnosis. Neurological examination is important to distinguish between cerebellar stroke and a more benign condition, since brain CT rarely identifies early-stage cerebellar infarction.[2] New imaging techniques like CT-P will contribute to the diagnosis. Rapid recognition of a cerebellar infarction and differentiation from more benign disorders presenting with vertigo, headache, dysarthria or vomiting, is crucial to achieve an optimal outcome with early treatment with intravenous alteplase.

References

1. *Cano L.M., Cardona P., Quesada H., et al. [Cerebellar infarction: prognosis and complications of vascular territories]. Neurologia. 2012; 27: 330-335.*
2. *Edlow J.A., Newman-Toker D.E., Savitz S.I. Diagnosis and initial management of cerebellar infarction. Lancet neurology. 2008; 7: 951-964.*
3. *Terao S., Miura N., Osano Y., et al. Multiple cerebellar infarcts: clinical and pathophysiologic features. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2005; 14: 193-198.*
4. *Hacke W., Donnan G., Fieschi C., et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004; 363: 768-774.*
5. *Hacke W., Kaste M., Bluhmki E., et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. The New England journal of medicine. 2008; 359: 1317-1329.*
6. *Wardlaw J.M., Murray V., Berge E., et al. Thrombolysis for acute ischaemic stroke. The Cochrane database of systematic reviews. 2009: CD000213.*
7. *Tomaszek D.E., Rosner M.J. Cerebellar infarction: analysis of twenty-one cases. Surgical neurology. 1985; 24: 223-226.*
8. *Ciccone A., Valvassori L., Ponzio M., et al. Intra-arterial or intravenous thrombolysis for acute ischemic stroke? The SYNTHESIS pilot trial. Journal of neurointerventional surgery. 2010; 2: 74-79.*
9. *Ogawa A., Mori E., Minematsu K., et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. Stroke; a journal of cerebral circulation. 2007; 38: 2633-2639.*
10. *Smith W.S. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. AJNR American journal of neuroradiology. 2006; 27: 1177-1182.*
11. *Smith W.S., Sung G., Starkman S., et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke; a journal of cerebral circulation. 2005; 36: 1432-1438.*

The relation between the GTF2I gene and positive emotionality in preschool children

A candidate gene study

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Abstract

Background: **One of the most fascinating clinical manifestations of Williams syndrome is positive emotionality. GFT2I, a gene deleted in Williams syndrome, has been recently associated with behavioural phenotypes, such as hyper-sociability. For clinical practice, this might provide interesting clues for the treatment of mood disorders. For example, if certain transcription factors related to positive emotionality could be manipulated pharmacologically, they could serve as potential targets against depression. The aim of this study is to examine the relationship between the GTF2I gene and positive emotionality in a sample of preschool-aged children, using data from the Generation R study.**

Methods: **A candidate gene study was performed using data on two single nucleotide polymorphisms (rs2267816 and rs7809575) and observational outcomes of 36-month old children (n=862). Observational outcomes included two episodes of the Laboratory Temperament Assessment Battery (Popping Bubbles and Puppet Game episodes). Associations between positive emotionality, genotype and gender were explored using linear regression models.**

Results: **We found no significant correlation between positive emotionality and the two SNPs of interest. However, we report a trend to positive emotionality during the Puppet Game episode and rs7809575 (β= 0.078, 95% CI (-0.002 – 0.173), p=0.056).**

Conclusions: No correlation between de GTF2I gene and positive emotionality was found. More research is needed to draw conclusions about the genetic contribution to positive emotionality.

Introduction

Williams syndrome (WS) is a rare, genetic, neurodevelopmental disorder with a prevalence of 1 in 7500.[1] In addition to characteristic facial features, clinical manifestations include mild to moderate intellectual disability and cardiovascular, endocrine and connective tissue disruptions. Furthermore, children with WS show characteristic personality features, such as hyper-sociability, increased empathy and positive emotionality.[3] The behavioural symptoms also include generalized anxiety and attention problems/ hyperactivity. [3,4] However, the most remarkable aspect of the disorder is positivity and exuberance.[5]

The genetic signature of WS is very well-defined, as a microdeletion of about 1.5 megabases of chromosome 7q11.23 [6] including, among others, the elastin gene (ELN),[7] LIMK1,[8] CYLN2,[9] (which regulates dynamic aspects of the cell cytoskeleton) and the GTF2I family genes.[10] The GTF21 family genes include GTF2I, GTF2IRD1 and GTF2IRD2. These genes encode transcription factors, which exert their function in many developmental pathways. This makes them strong candidates for the neurological symptoms of WS.[11]

We hypothesize that GTF2I may have an effect on the variation of positive emotionality in a non-clinical population. Two single nucleotide polymorphisms (SNPs), rs2267816 and rs7809575, residing in intronic areas of GFT2I may have a functional impact by creating different splice variants.

To examine the effects of these two SNPs in a sample of 36-month old children, data from the Generation R Study was used. This is a prospective cohort study that follows children in Rotterdam from fetal life to adulthood.[12]

The goal of this study is to identify possible biological pathways determining positive emotionality levels in children. The association between the SNPs and positive emotionality would contribute to the understanding of normal and distorted behaviour. This might have an impact on treatment of mood disorders. If certain transcription factors related to positive emotionality could be manipulated pharmacologically, they could serve as potential targets against depression.

Therefore the aim of this study was to examine the relationship between the GTF2I gene and positive emotionality in a sample of 36-month old children, using data from the Generation R study.

Methods

Patients

This study was embedded in the Generation R Study, which comprises children born between April 2002 and January 2006. The 5-year follow-up data were available for 8305 children. The data used in this study were collected at 36-month follow-up of a focus cohort (n=862, males 51%) from the Generation R population. Data collected in these follow-up sessions included observational measurements, a physical examination, questionnaires and a bacterial carriage test.[12]

This study has been approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from parents of all participating children.

All children of the Generation R Focus Study are of Dutch national origin, defined as having two parents and four grandparents born in the Netherlands. DNA was obtained from cord blood samples at birth. Children in the Focus group had no major disorders.

Genotyping and quality control

The two SNPs in this study were extracted from the genome-wide data of Generation R, obtained using high-density SNP arrays on Illumina platforms. Illumina microarrays provides the possibilty of large scale genotyping of more than 450,000 sites across the genome. By the use of bioinformatic tools (PLINK), it was possible to extract information on the two SNPs of interest. For each participant, information was available on the status of the two SNPs, and coded as 0= homozygous for the minor allele, 1= heterozygous, 2= homozygous for the major allele. Before imputation, SNPs with minor allele frequency of <1%, call rate <95% or Hardy–Weinberg equilibrium $p<1 \times 10^{-6}$ were excluded. Samples were also excluded if they contained duplicates, excess heterozygosity, non-European ancestry or ambiguous gender. Imputation was performed using MACH for roughly 2.5 million SNPs against HapMap Phase II (release 22). Imputed SNPs were filtered prior to meta-analysis to exclude poorly imputed SNPs (MACH filter r2< 0.3).

Study procedures

At 36 months, children visited the Erasmus MC in whom positive emotionality was assessed using two episodes from the Laboratory Temperament Assessment Battery (Lab-TAB), the puppet game and popping bubbles.[13]

The Lab-TAB is a widely used standardized instrument for the observational assessment of early temperament. It comprises a set of 3 to 5 minute episodes that simulate everyday situations. In our case the popping bubble and the puppet game test are applied to observe the individual differences in the expression of emotion (low, high or in between). The Popping Bubbles episode is divided in two tasks, in which both low and high pleasure are measured. The expression of happiness, for example the intensity of smiling or laughter, is scored, first only when the experimenter demonstrates a bubble gun and gives the child the toy (low pleasure), and secondly when the child is given the opportunity to chase and 'pop' the bubbles (high pleasure). Scores varied between 0 and 3. For example when scoring the intensity of smiling, 0 = no smiling at all and 3 = large smile, with lips stretched broadly and quite upturned. The same applies to the Puppet Game. The Puppet Game episode measures enjoyment in response to social stimulation by using puppets talking to the child in a set dialogue. The way the child reacts to tickling is scored as well.

The scores of both 'Popping Bubbles' and 'Puppet Game' are continuous. Averages were computed for each child response or parameter across epochs. Inter-rater reliability (Intra-Class Correlation Coefficient (ICCs) single measures) in this study for these averages were 0.73 (95% CI 0.71-0.75) for the Popping Bubbles and 0.81 (95% CI 0.66 - 0.95) for the Puppet Game.

Statistics

All statistical analyses were performed using the Statistical Package for Social Sciences Version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Associations between positive emotionality, genotype and gender were explored using linear regression models, assuming an additive genetic model. A bivariate correlation test was performed between the Popping Bubbles and the Puppet Game to examine the similarity of the outcome of the two tests.

Results

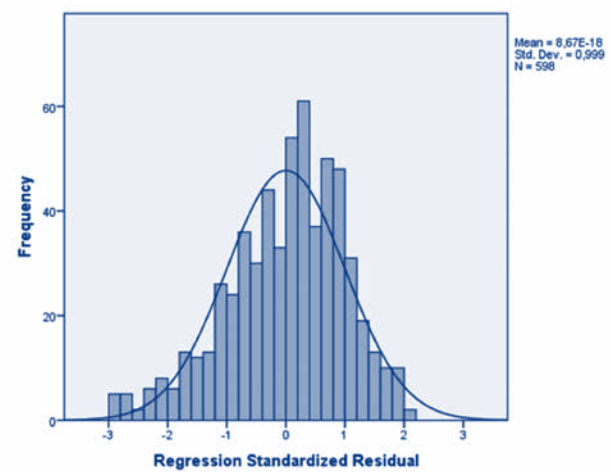
Significant correlations were found between all four episodes of Lab-TAB, which were used to estimate positive emotionality (table 1). The highest correlation was found between the low-high pleasure and low pleasure groups. All results were normally distributed, ensuring significant sample variation, which is important for genetic studies (figure 1). Also, no significant differences in the levels of positive emotionality between girls and boys were found (results not shown).

Table 1 - Correlations between episodes of Lab-TAB, measuring positive emotionality in 36-month old children

Episode (z-scores)		Low pleasure	High pleasure	Low-high pleasure	*Pleasure
Low pleasure	Pearson correlation (p-value)	-	0,393** (0,000)	0,861** (0,000)	0,216** (0,000)
High pleasure	Pearson correlation (p-value)	0,393** (0,00)	-	0,821** (0,000)	0,323** (0,000)
Low-high pleasure	Pearson correlation (p-value)	0,861** (0,000)	0,821** (0,000)	-	0,326** (0,000)
***Pleasure**	Pearson correlation (p-value)	0,216** (0,000)	0,323** (0,000)	0,326** (0,000)	-

*. Episodes of Puppet Game, all other episodes are of the Popping Bubbles.
**. Correlation is significant at the 0.01 level (2-tailed).

Figure 1:
Distribution of the Puppet Game episode, in the Generation R sample



When performing the linear regression with both the Popping Bubbles and the Puppet Game on the two SNPs (rs7809575 and rs2267816), no significant correlation was found (table 2 and 3). However, there was a trend to significance in positivity scores in the Puppet Game for rs7809575: β 0.078 (95% CI -0.002 – 0.173, p0.056).

Table 2 - ANOVA of rs7809575 and positive emotionality episodes

Test	Episode	β	95% CI	P-value
Popping	Low pleasure	0.010	-0.078 – 0.099	0.815
Bubbles	High pleasure	0.056	-0.023 – 0.130	0.168
	Low-high pleasure	0.029	-0.045 – 0.095	0.481
Puppet Game	Pleasure	0.078	-0.002 – 0.173	0.056

Table 3 - ANOVA of rs2267816 and positive emotionality episodes

Test	Episode	β	95% CI	P-value
Popping	Low pleasure	-0.003	-0.093 – 0.087	0.950
Bubbles	High pleasure	0.052	-0.028 – 0.128	0.205
	Low-high pleasure	0.026	-0.048 – 0.094	0.529
Puppet Game	Pleasure	0.035	-0.050 – 0.129	0.387

Discussion

In this population based study, we investigated a correlation between positive emotionality of 36-month old children and the common polymorphisms of GTF2I genes (rs2267816 and rs7809575). Although no significant results were found, we did find a trend to significance for rs7809575 on the Puppet Game for the additive model (p=0.056). We did not expect to find any differences between genders, because the GTF2I is an autosomal gene. Indeed, no significant association between gender and positive emotionality was found; 36-month old boys and girls show equal levels of positive emotionality. This supports our hypothesis.

A comparison of the results with other studies is not possible given the fact that to our knowledge, this was the first study examining the correlation between positive emotionality and the GTF2I genes. By following biological evidence derived from a clinical syndrome (WS), we increased our prior probability of detecting true associations, in a population based sample of 36-month old children.

Some elements in our methods may have influenced our results. For example, it can be argued whether the observational tests provide a valid representation of the overall positive emotionality of a child, or assess the happiness at that specific time point. By using questionnaires with parent ratings, emotions are scored over a longer period in time. However, by using observational methods, several potential biases that are likely to occur when using questionnaires with parent ratings, are prevented.[13]

According to sample size estimations using LLC statistical solutions, our population size was adequate to provide enough power for statistical analysis. However, if the effects of the SNPs had been smaller than estimated (<1%), a larger sample size would have been needed.

It is also possible that the GTF2I gene indeed correlates with positive emotionality, but that we did not select the SNPs with the greatest impact. More polymorphisms can be researched and a risk score can be estimated for possible associations with levels of positive emotionality.

Moreover, all children participated in our study are of Dutch origin, which provides a homogeneous population. The homogeneity of the population is a great advantage in genetic research, but can also cause difficulties when the results are generalized to other populations.

Although positive emotionality of WS children might be influenced by genetics, it is questionable whether this happy behaviour is non-pathological or a form of pathological positivity. This pathological positivity could differ from the happiness present in the non-clinical population. As non-pathological positivity is multifactorial, it might be influenced by environmental factors and be subjected to epigenetic regulation as well. Since the influence of one particular SNP on the positivity in the general population is presumably very limited, detecting these small effects is challenging.

Conclusion

This study has not yielded evidence on the correlation between the GTF2I gene and positive emotionality of 36-month old children. However, a trend to significance was found for rs7809575 and positivity during the Puppet Game episode. More research is necessary to reach a conclusion about the genetic contribution to positive emotionality. Future steps will be estimating a risk score of the GTF2I gene, studying the expression levels of GFT2I between cases and controls and examining the contribution of epigenetic regulation in this chromosomal area. In the long-term, these efforts are promising to provide more insights on the pathways of positive emotionality.

References

1. *Stromme, P., Bjornstad, P.G., Ramstad, K., Prevalence estimation of Williams syndrome. J Child Neurol. 2002; 17: 269-71*
2. *Martens, M.A., Wilson, S.J., Reutens, D.C., Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. J Child Psychol Psychiatry. 2008; 49: 576-608*
3. *Einfeld, S.L., Tonge, B.J., Florio, T., Behavioral and emotional disturbance in individuals with Williams syndrome. Am J Ment Retard. 1997; 102: 45-53*
4. *Greer, M.K., Brown, F.R., et al., Cognitive, adaptive, and behavioral characteristics of Williams syndrome. Am J Med Genet. 1997; 74: 521-5*
5. *Jarvinen, A., Korenberg, JR., Bellugi U., The social phenotype of Williams syndrome. Curr Opin Neurobiol. 2013; 23: 414-22*
6. *Peoples, R., Franke, Y., Wang, YK., et al., A physical map, including a BAC/PAC clone contig, of the Williams-Beuren syndrome--deletion region at 7q11.23. Am J Hum Genet. 2000; 1: 147-68*
7. *Ewart, A.K., Morris, C.A., Atkinson, D., et al., Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. Nature Genet. 1993; 5: 11-6*
8. *Meng, Y., Zhang, Y., Tregoubov, V., et al., Abnormal spine morphology and enhanced LTP in LIMK-1 knockout mice. Neuron. 2002; 35: 121-33*
9. *Hoogenraad, C.C., Koekkoek, B., Akhmanova, A., et al., Targeted mutation of Cyln2 in the Williams syndrome critical region links CLIP-115 haploinsufficiency to neurodevelopmental abnormalities in mice. Nature Genet. 2002; 32: 116-27*
10. *Tassabehji, M., Hammond, P., Karmiloff-Smith, A., et al., GTF2IRD1 in craniofacial development of humans and mice. Science. 2005; 310: 1184-7*
11. *Porter, M.A., Dobson-Stone, C., Kwok, J.B., et al., A role for transcription factor GTF2IRD2 in executive function in Williams-Beuren syndrome. PloS one. 2012; 7(10):e47457*
12. *Jaddoe, V.W., van Duijn, C.M., Franco, O.H.,The Generation R Study: design and cohort update 2012. Eur J Epidemiol. 2012; 27: 739-56*
13. *Gagne, J.R., Van Hulle, C.A., Aksan, N., et al., Deriving childhood temperament measures from emotion-eliciting behavioral episodes: scale construction and initial validation. Psychol Assessment. 2011; 23: 337-53*

The association between knee joint shape and osteoarthritis development in middle-aged, overweight and obese women

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Summary

Objective: **Objective: To investigate whether knee shape is predictive for the development of knee osteoarthritis (OA) after 2.5 years follow-up in women between 50 and 60 years with a BMI ≥ 27 kg/m2 at baseline. Methods: Using Statistical Shape Models (SSM), the shape of the femur, tibia and fibula on radiographs was quantified in 407 women (814 knees) without clinical and radiographic OA at baseline. Data was obtained from three sources: magnetic resonance imaging (MRI) to semi-quantitatively score the baseline and follow-up OA features (MOAKS), radiographs to score the Kellgren & Lawrence (K&L) grading and questionnaires to asses pain. Results: After excluding the knees with a K&L-score of ≥ 2 at baseline, 393 women (756 knees) remained. The first 17 stable modes were used for the analysis. Mode 7 showed a statistically significant association on the progression of medial meniscal extrusion (Odds ratio (OR), 0.664 [95% CI, 0.533 to 0.827]), after adjustment for multiple testing. The shape variant of mode 7 represented a narrow tibial plateau and femoral epicondyles, a narrow notch, raised edges at the outer surface of the tibial plateau and the tibial spines standing close to each other. Conclusions: Within the high risk group of middle-aged overweight women, relative narrow knees seem more at risk for the development of knee OA.**

Introduction

Knee osteoarthritis (OA) is a common health issue nowadays, particularly in the elderly and in females [1,2]. The global age-standardized prevalence of knee OA was 3.8% between 1990-2010 [1]. One of the major risk factors for the development of knee OA is obesity [3-6]. Knee OA will become a bigger issue for the health care systems in the coming years because of the aging and increasing obesity of the population, especially in high-income regions as North America and Western Europe [1].

Radiographic knee OA is almost four times higher in obese women than in those with normal BMI [4]. This increased risk could have both a mechanical as well as a systemic component. In individuals with an increased body mass index (BMI ≥ 25 kg/m2), there is an increased load on both the medial and lateral compartment of the knee compared to individuals with a normal BMI (< 25 kg/m2) [3,4]. The increased knee load in obese individuals results in higher diurnal strain in the cartilage of both the medial and lateral compartment of the tibia, which may explain their increased risk of OA [7].

Obesity is also associated with metabolic syndrome. This syndrome is associated with alterations in cartilage metabolism and likely causes a low grade inflammation of the joint [8-10], which could lead to degradation of joint cartilage [9] and thus explain the increased risk of knee OA among obese women.

Although there are many treatments that target symptoms of OA, there is no evidence that they inhibit the progression of the degeneration of the joint [11,12]. Currently, OA is diagnosed in a late stage of the disease. Early detection could be helpful for the diagnostic process and the establishment of early intervention studies [13]. Changes in the shape of the bones forming the knee joint could be used for the early detection of OA [14,15].

Previous studies have shown that there is a strong relationship between the shape of the knee joint and the presence of OA [11,14,15]. Overall, widening and enlargement of the femur, narrowing of the joint space and a wider and elevated tibial plateau were seen in patients with OA [6,11,14,15]. If there is a possibility to identify in which knees these shape changes will occur, then there may be a possibility to identify knees which are at risk to develop OA and to detect OA in an early stage.

To investigate whether knee shapes are predictive for or cause the development of OA, a longitudinal study is necessary because most of the previously mentioned studies are not able to provide information on whether the shape is the cause or a consequence of OA due to their cross-sectional design. Therefore, the purpose of this study was to investigate whether certain knee shapes are predictive of incidence and progression of OA features at follow-up, in a high-risk group of middle-aged, overweight and obese women.

Methods

Population

Data from the PROOF study (PRevention of knee Osteoarthritis in Overweight Females, IS RCTN 42823086) was used [16]. The PROOF study was a preventive randomized controlled trial, which investigated the effects of a diet and exercise program and of glucosamine sulphate (double blind and placebo-controlled) on the incidence of knee OA after 2.5 years of follow-up.

The population in the PROOF study included women with a reported BMI ≥ 27 kg/m2 between 50 and 60 years of age, recruited from 50 general practitioners in the region of Rotterdam, the Netherlands. Additionally, the women had to be free of knee OA according to the ACR-criteria [17], were not undertreatmentforkneecomplaints,freeofMRIcontraindications, free of rheumatic diseases, did not use walking aids, mastered the Dutch language, had not used oral glucosamine for the last 6 months and had no major co-morbidities [16].

Study procedures and definitions

Semi-flexed (20°) posterior-anterior knee radiographs were taken at baseline and follow-up according to the MTP (Metatarsophalangeal) protocol [18]. Both feet were in 7.5° exo-rotation next to the measurement device and the joint space had to be in line with the X-ray beam. The radiographs of baseline and follow-up were scored by a trained researcher blinded for clinical outcomes (sequence known), using the Kellgren & Lawrence (K&L) criteria [19].

Radiographs were used to quantify the shape of the knee joint, by using Statistical Shape Modeling (SSM toolkit, Manchester University, UK) [20]. A statistical shape model of the tibia, fibula, femur and medial femoral condyle was constructed on the radiographs, by placing 75 landmark points along the contours of these structures (24 points on the tibia, 27 on the femur plus 8 on the medial condyle, and 16 on the fibula). Left knees were mirrored onto the right in order to create one shape model for both knees.

The contours were adjusted for size and rotation. By Principal Component Analysis, independent modes of shape variation in femur and tibia were produced. The resulting shape model consists of several modes, each mode showing the variation in a specific shape variant compared to the average, with negative and positive values representing the deviation from the mean. The number of modes was initially selected such that 90% of the shape variation in the study population was described.

To test the stability of the modes, bootstrapping was used to generate 1000 new datasets, each with the same number of knees and women, from which 1000 shape models were derived. By comparing the variability between these shape models, the stability of the modes can be assessed. This process was repeated using a dataset in which all points were set randomly, to get a measure of the variability of shape modes that are pure noise. Only the modes that showed less variability than the noise modes were retained.

The variability in each mode was assessed by calculating the angle between each bootstrap instance of the vector that represent a specific mode and the average mode, and by calculating the correlation between all bootstrap instances of each mode. This was done for the points on the real pictures and for a data set, where the points are completely random. All modes were retained for which the variation in angle was smaller and the correlation was higher than for the modes based on pure noise [21].

Participants filled in questionnaires at baseline and after 2.5 years to determine the knee pain, defined as knee pain in the last 12 months and on most of the days in the last month.

MRI of both knees, were taken at baseline and after 2.5 years at follow-up, on a 1.5 Tesla scanner. The MRI protocol included coronal and sagittal proton density weighted sequences (slice thickness 3.0 mm/ slice gap 0.3 mm), a coronal T2-weighted Spectral Presaturation by Inversion Recovery sequence (slice thickness 5.0 mm / slice gap 0.5 mm), an axial dual spin-echo sequence (slice thickness 4.5 mm / slice gap 0.5 mm), and a sagittal 3D water selective sequence with fat saturation (slice thickness 1.5mm) [22].

The MRIs were scored at baseline and follow-up, individually at the same time by two trained readers and a musculoskeletal radiologist using a semi quantitative MRI Scoring tool, the MRI Osteoarthritis Knee score (MOAKS) [22,23]. The definition of progression, no change or improvement of the individual MOAKS features are given elsewhere [22]. The following MOAKS features were used for the present study; bone marrow lesions (BML), cartilage defects (CART), osteophytes (OST), meniscal pathologies (MEN) and meniscal extrusions (MENext). For each of the 14 MOAKS sub regions, progression of a feature from baseline to follow-up was defined as -1 for improvement in that feature; 1 for deterioration and 0 for no change. The summed progression scores of the MOAKS features within the medial and the lateral compartment of the knee were used, whereby an accumulated score ≥1 indicated progression of disease and < 1 was indicative of improvement /no change.

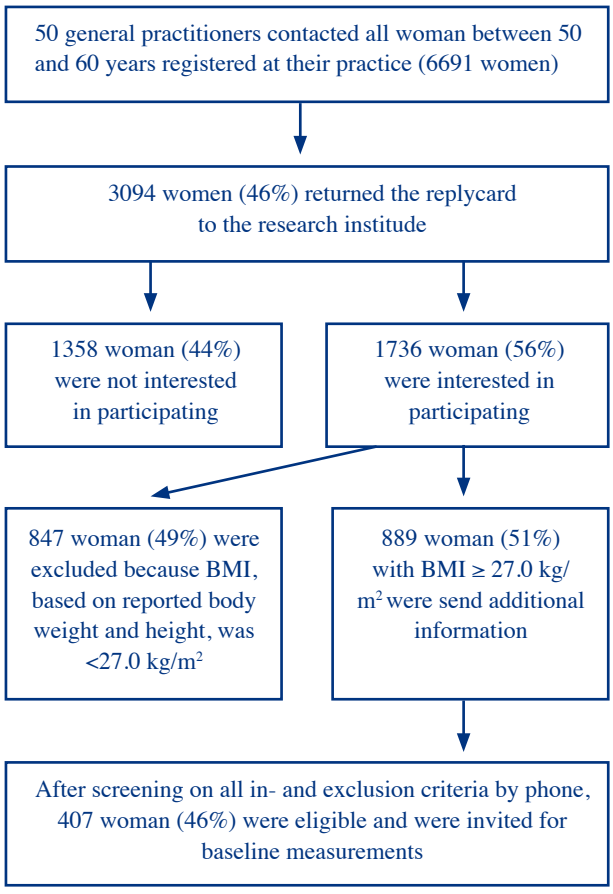
Statistics

Only women with a complete follow-up and with bilateral K&L-scores < 2 were used in the present study. To test whether the included cohort was different from the original cohort of the PROOF study, the mean age and BMI of both group were compared using appropriate statistics, based on the distribution of the data.

To determine the reliability of the statistical shape modes, 20 knee radiographs were scored twice and intra-observer reproducibility was calculated by means of intraclass correlation coefficient.

To test whether certain knee shapes were predictive of incidence and progression of early OA features, the association between the corresponding mode values and OA criteria (incidence of K&L ≥ 2, incidence of chronic pain and the progression MOAKS scores) was determined using Generalized Estimating Equations (GEE). The GEE takes the correlation between the left and right knees within subjects into account and was adjusted for BMI, age and K&L score at baseline. Furthermore, to adjust for multiple testing, the significance threshold of $p < 0.05$ was divided by the number of modes we tested. Before the GEE was performed, a z-transformation of every mode was made to normalize the variance for each mode. All tested were performed using SPSS 21.0 (SPSS Inc., Chicago, IL).

Figure 1- Study selection



Results

50 general practitioners contacted a total of 6691 women. Eventually, 407 women were invited for baseline measurements. Figure 1 shows the complete flowchart.

The knees with a Kellgren and Lawrence [19] score of ≥ 2 at baseline were excluded, whereupon 756 knees remained. Table 1 shows the characteristics of these women. Baseline characteristics of the women from the cohort (407 women, number of knees = 814) and the included cohort, selected for the present study (393 women, numbers of knees = 756) were not significantly different (age 55.7 ± 3.2 year, BMI was 32.4 ± 4.3 kg/m2 vs. 55.7 ± 3.2 year, 32.0 ± 3.9 kg/m2 respectively, Page = 0.116, PBMI = 0.878).

Progression of bone marrow lesions were found medially in 8% (51/640) and laterally in 6% (37/640) of all knees. Cartilage defects progressed in 8% (48/639) medially and 5% (33/639) laterally and osteophytes medially 10% (62/639) vs 4% (24/639) laterally. Meniscal pathology progression was scored medially in 21% (132/634) and laterally in 11% (67/634) knees and meniscal extrusion in 14% (92/635) medially and 3% (21/637) laterally. Incidence of K&L-grade ≥ 2 was found in 5% (36/666) of all knees. Incidence of chronic pain was found in 7% (44/658) of the subjects.

The Statistical Shape Modeling produced 35 modes. After the bootstrapping and selection procedure, 17 stable modes were retained. The average intraclass correlation coefficient of the 17 stable modes was 0.837, with a range of 0.668 – 0.995. Highly reliable repeatability is considered to be a score of ≥ 0.80, a condition that was met in 11 of the 17 stable modes.

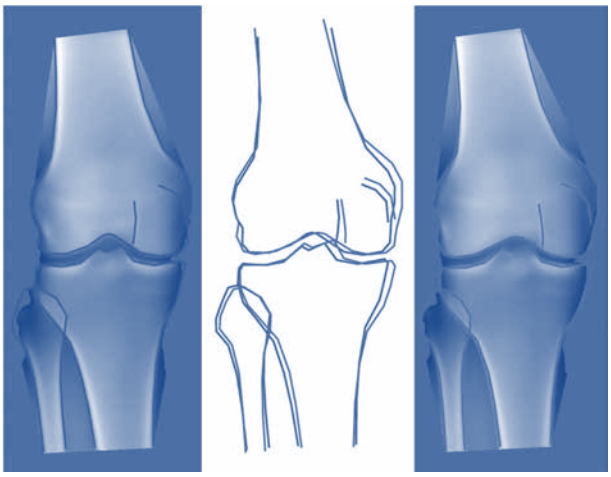
After adjustment for multiple testing, a result was considered significant with a P-value lower than 0.0029. Only mode 7 showed a statistically significant association with the progression of medial meniscal extrusion (P = 0.00026). All associations between the 17 modes and the outcome measures are shown in Table 3.

Table 1. Baseline characteristic (mean ± sd)

	Cohort	Selected cohort
Women, No.	407	393
Age, yr.	55.7 ± 3.2	55.7 ± 3.2
BMI	32.4 ± 4.3	32.0 ± 3.9
WOMAC pain (0-100)	6.78 ± 11.21	6.25 ± 10.65
WOMAC function (0-100)	6.69 ± 11.10	6.23 ± 10.46
Injury, # knees	101 (12.4%)	85 (11.2%)
Knees, No.	814	756
K&L score		
Grade 0	412/810 (50.9%)	412/756 (54.5%)
Grade 1	344/810 (42.5%)	344/756 (45.5%)
Grade ≥2	54/810 (6.7%)	-

The original cohort selected in the PROOF study and our selected cohort characteristics are shown above. We excluded the knees which already have OA according to the Kellgren and Lawrence criteria.

Figure 2- Shape Model Mode 7



Mode 7 associates with the presence of early OA signs (+/- 4 SD; to illustrate relatively small differences within modes properly). Lower values (left side) are predictive for the development of knee OA. The direction of Mode 7 resprents a relatively narrow knee combined with a narrow tibial plateau and femoral epicondyles, a relatively wider femoral and tibial shaft, a narrow notch, raised edges at the outer surface of the tibial plateau and the tibial spines that stand close to each other.

Discussion

In this study it was investigated whether certain knee shapes were associated with the progression of OA features on MRI and the incidence of radiographic knee OA, in a high-risk group of overweight and obese women. Out of the 17 modes of shape variation, only mode 7 was associated significantly to progression of medial meniscal extrusion.

The shape within mode 7 seemed to represent a relatively narrow knee combined with a narrow tibial plateau and femoral epicondyles, a relatively wider femoral and tibial shaft, narrowing of the notch, raised edges at the outer surface of the tibial plateau and the tibial spines seem to stand closer to each other (see Figure 2).

Contrary to our findings, earlier research showed a general widening of the tibial plateau and femoral epicondyles in OA knees [14,15]. However, these findings were all in individuals with established knee OA, while our study investigated those at risk of getting knee OA. Widening of knees could be a consequence of OA and possibly serves as a mechanism to distribute the load and thus lower the stress on cartilage in knees with OA.

Our finding that a relatively narrow knee is predictive of knee OA might point to the harmful effect of relatively high stresses in the cartilage. In a knee with a relatively narrow tibial plateau and femoral epicondyles there will be a higher stress on the surface of the weight-bearing knee joint, compared with a wider knee joint. This higher cartilage stress may induce more cartilage defects and thereby contribute to the elevated risk of OA in a relatively narrow knee [7]. The combination of a relatively narrow knee and having obesity, results in an even higher load, because the load on the weight-bearing knee joint in women with a BMI ≥ 27 kg/m2 is also higher than in women with a BMI < 27 kg/m2 [3,4], which elevated the risk of OA even more.

Mode 7 also showed raised edges at the outer surface of the medial tibial plateau, which may explain the association with the progression of medial meniscal extrusion. The raised edges at the outer surface results in a narrower space for the menisci which may increase the risk of developing meniscal tears. Especially in women with a high BMI, the higher load on the joint could lead to more stress on the menisci. The presence of meniscal tears is a risk factor for medial meniscal extrusion [24], which is associated with the progression of knee OA [25].

The shape variation of mode 7 also showed changes in other aspects of the knee shape, which presumably are related to the narrow knee. The narrow knee seems to go together with the tibial spines standing close to each other and with a narrow notch. Possibly, not only the narrowness of the knee itself, but also these specific aspects could have an influence on the development of OA. Changes in the tibial spines are described in knees with OA, particularly more spiking tibial spines are typical for OA [15,26,27]. The tibial spines standing closer to each other has been reported in combination with osteophytes presence [26], which is interesting because in this study an association with progression of osteophytes medially was found. The narrow notch results in a smaller cross-sectional area of the anterior cruciate ligament (ACL) midsubstance, which may possibly cause damage of the cruciate ligaments [28,29] which is a known risk factor for OA [30].

In addition, several other modes were associated with the progression and the incidence of OA features, although, none reached significance after correcting for multiple testing. Not every mode demonstrated a clear shape variant, some appeared to represent rotation of the knee joint, some showed variation in joint space width and others seemed to show changes in position of the fibula, which is not an official part of the knee joint. The question remains whether these shape variants may be relevant, because after adjustment for multiple testing there were no significant associations.

The PROOF study investigated the effects of a diet and exercise program and or glucosamine sulphate use on the incidence of knee OA. No significant main effects of the diet and exercise program and of glucosamine sulphate on incident knee OA in middle-aged women with a BMI ≥ 27 kg/m2 were found over 2.5 years. However, positive trends for the two separate interventions were found [31]. Therefore, the influence these interventions may have had on the results was assessed. There were no significant differences in the results after testing the four intervention groups separately or after adjustment for the interventions.

A drawback of our study is that data are limited to women with a BMI ≥ 27 kg/m2. The results of our study may not be representative for individuals with a BMI < 27 kg/m2 and may also not be applicable to males or even for individuals outside the 50-60 yrs age range. However, for the short follow-up of 2.5 years, a high-risk population was needed to get progression of OA features at follow-up measurements. A BMI ≥ 27 kg/m2 and the female sex is associated with a high-risk of developing knee OA, due to accompanying inflammation of the knee joint as well the increased load on both the medial and lateral compartment of the knee compared to individuals with a low BMI [7,9,32].

Table 2. Results for GEE of mode values on presence of early OA signs

	Pain		KL inc		BML med prog		BML lat prog		CART med prog		CART lat prog	
	P	ORII	P	ORII	P	ORII	P	ORII	P	ORII	P	ORII
M0	0.572	1.099	0.118	1.037	0.857	1.026	0.189	1.239	0.180	1.263	0.322	1.207
M1	0.686	1.064	0.194	1.254	0.741	1.047	0.646	1.092	0.209	1.188	0.611	1.108
M2	0.607	1.087	0.735	1.057	0.185	1.204	0.309	1.193	0.409	1.137	0.132	1.432
M3	0.461	0.888	0.297	1.227	0.703	0.937	0.154	1.339	0.391	1.180	0.483	0.858
M4	0.156	1.263	0.236	0.779	0.494	0.900	0.072	1.487	0.622	1.089	0.955	1.013
M5	0.124	1.310	0.690	1.084	0.826	1.040	**0.017**	1.469	0.282	0.844	0.678	1.107
M6	0.295	1.243	0.065	0.723	0.842	1.032	0.883	0.974	0.895	0.981	0.616	1.078
M7	0.308	1.208	**0.017**	0.634	0.752	0.945	0.151	0.753	0.268	0.850	0.410	1.219
M8	0.186	1.275	0.367	0.876	0.229	0.805	0.846	1.033	0.692	0.945	0.142	1.341
M9	0.213	0.794	0.923	1.017	0.805	1.040	0.561	0.896	0.633	0.941	0.842	1.039
M10	0.959	1.007	0.204	0.792	**0.017**	0.660	0.643	0.917	0.198	0.819	0.610	1.114
M11	0.846	0.965	0.280	0.825	0.522	0.903	0.706	1.063	0.364	0.869	0.346	0.840
M12	0.314	0.849	0.463	0.871	0.411	0.887	0.754	1.057	0.830	1.037	0.823	0.944
M13	**0.043**	1.417	0.902	1.020	0.505	1.126	0.896	1.020	0.294	0.854	0.203	0.790
M14	0.154	0.796	0.357	0.849	0.612	1.087	0.067	0.708	0.069	1.301	0.056	0.763
M15	0.718	0.953	0.340	1.206	0.761	1.055	0.525	1.103	0.608	0.916	0.061	0.695
M16	0.671	0.928	0.981	1.005	**0.026**	1.429	0.166	0.803	0.443	0.876	0.123	0.730

PAIN: pain in the last 12 months and on most of the days in the last month; KLinc: Kellgren and Lawrence incidence defined as K&L score of every knee at baseline ≤ 1 and with a K&L score ≥ 2 at follow-up; the MOAKS progression scores of BML: bone marrow lesion; CART: cartilage defects; OST: osteophyte; MEN: meniscal pathologies; MENext: meniscal extrusion; med: medial compartment of the knee and lat: lateral compartment of the knee. I Adjusted for BMI, Age and K&L baseline ≥1. II Odds ratio based on z-scores of the mode values. .**Bold.** 90%-CI represent statistically significant results (P < 0,05). .**Bold.** represent statistically significant P-values after adjustment of multiple testing (p < 0.00294).

Table 2. Results for GEE of mode values on presence of early OA signs

	OST med prog		OST lat prog		MEN med prog		MEN lat prog		MENext med prog		MENext lat prog	
	P	ORII	P	ORII	P	ORII	P	ORII	P	ORII	P	ORII
M0	0.930	0.988	0.402	1.127	0.273	0.899	0.367	0.896	**0.019**	1.319	0.483	0.859
M1	0.079	1.326	**0.030**	1.531	0.464	0.925	0.436	0.907	0.945	0.991	0.825	1.054
M2	0.173	1.249	0.443	0.794	0.954	1.005	0.072	1.297	0.344	0.896	0.456	0.860
M3	0.775	0.955	**0.040**	1.628	0.511	0.941	**0.015**	1.343	0.126	1.191	0.652	1.090
M4	0.131	0.772	0.804	1.075	0.187	1.137	0.235	1.192	0.619	0.943	0.638	0.917
M5	0.822	1.032	0.653	0.888	0.102	1.172	0.204	1.175	0.736	1.037	0.340	1.231
M6	0.106	0.795	0.455	0.872	0.305	1.115	0.516	0.914	0.977	0.997	0.886	0.973
M7	**0.031**	0.736	0.078	0.669	0.767	0.971	0.207	0.848	**0.000**	0.664	0.989	1.003
M8	0.581	1.088	0.286	0.830	0.219	1.131	0.584	1.074	0.134	0.838	0.541	1.162
M9	0.767	1.038	0.751	0.913	0.279	0.906	0.061	0.772	0.449	0.917	0.138	0.741
M10	0.747	0.952	0.717	0.925	0,359	1.094	0.637	0.944	0.387	0.901	0.184	0.807
M11	0.674	1.051	0.411	0.870	0.274	1.124	0.776	1.036	0.794	0.971	0.791	1.061
M12	0.976	0.995	0.818	1.072	0.886	1.013	0.778	0.967	0.700	1.044	0.234	0.764
M13	0.357	1.135	0.571	0.899	0.632	0.953	0.058	0.763	0.578	0.942	0.795	1.069
M14	0.302	1.146	0.140	1.350	0.359	0.915	0.193	0.848	0.277	1.135	0.075	1.440
M15	0.800	1.031	0.659	0.919	0.177	0.878	**0.018**	1.347	0.554	1.071	0.129	1.383
M16	0.812	1.037	0.744	0.934	0.575	1.057	0.983	1.003	0.826	1.030	0.544	1.133

PAIN: pain in the last 12 months and on most of the days in the last month; KLinc: Kellgren and Lawrence incidence defined as K&L score of every knee at baseline ≤ 1 and with a K&L score ≥ 2 at follow-up; the MOAKS progression scores of BML: bone marrow lesion; CART: cartilage defects; OST: osteophyte; MEN: meniscal pathologies; MENext: meniscal extrusion; med: medial compartment of the knee and lat: lateral compartment of the knee. I Adjusted for BMI, Age and K&L baseline ≥1. II Odds ratio based on z-scores of the mode values. .**Bold.** 90%-CI represent statistically significant results (P < 0,05). .**Bold.** represent statistically significant P-values after adjustment of multiple testing (p < 0.00294).

Still, in this high risk group, there was a limited number of medial and especially, lateral progression of the MOAKS features. This can explain why only a single significant result was found after adjustment for multiple testing.

Furthermore, there is still a chance of a residual type 1 error because the p-values were only adjusted for the number of modes, but given the exploratory nature of this study this is taken for granted.

In contrast to earlier cross-sectional studies, a 2.5 year prospective study was conducted in individuals without OA according to the K&L criteria at baseline [19] to investigate whether certain knee shapes were predictive of incidence and progression of early OA features. Cross-sectional studies could not provide information on whether the shape is the cause or a consequence of OA. Our longitudinal study design on the other hand, showed that the OA knee shape precedes OA. Thus, our

data indicate that a relatively narrow knee could be a cause for the development of OA in middle-aged, overweight and obese women, without established OA.

In conclusion, this study has shown that within the high risk group of middle-aged overweight and obese women, some women are at higher risk. These women have the following knee shape characteristics: a relatively narrow knee combined with a narrow tibial plateau and femoral epicondyles, a relatively wider femoral and tibial shaft, a narrow notch, raised edges at the outer surface of the tibial plateau and tibial spines that stand close to each other. These knee shape characteristics appear to play a role in the development of early OA features. Early detection of this high-risk group is important, therefore further studies are required to verify the current findings and investigate the real dimensions of the knee joint on radiographs or MRI scans. With the results of these studies an early detection method could be developed providing an opportunity to conduct early intervention studies in a more efficient way. This in turn could provide information on which interventions or therapies have the potential to delay the development of OA or slow down the progression.

References

1. *Cross M., Smith E., Hoy D., et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Annals of the Rheumatic Diseases. 2014: Epub 2014/02/21.*
2. *Busija L., Bridgett L., Williams S.R.M., et al. Osteoarthritis. Best Pract Res Cl Rh. 2010; 24: 757-768.*
3. *Coggon D., Reading I., Croft P., et al. Knee osteoarthritis and obesity. Int J Obesity. 2001; 25: 622-627.*
4. *Manek N.J., Hart D., Spector T.D., et al. The association of body mass index and osteoarthritis of the knee joint - An examination of genetic and environmental influences. Arthritis Rheum. 2003; 48: 1024-1029.*
5. *Reijman M., Pols H.A.P., Bergink A.P., et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: The Rotterdam Study. Annals of the Rheumatic Diseases. 2007; 66: 158-162.*
6. *Ding C., Cicuttini F., Scott F., et al. Knee structural alteration and BMI: a cross-sectional study. Obes Res. 2005; 13: 350-361.*
7. *Widmyer M.R., Utturkar G.M., Leddy H.A., et al. High Body Mass Index Is Associated With Increased Diurnal Strains in the Articular Cartilage of the Knee. Arthritis Rheum. 2013; 65: 2615-2622.*
8. *Hanna F.S., Bell R.J., Davis S.R., et al. Factors affecting patella cartilage and bone in middle-aged women. Arthrit Rheum-Arthr. 2007; 57: 272-278.*
9. *Guilak F. Biomechanical factors in osteoarthritis. Best Pract Res Cl Rh. 2011; 25: 815-823.*
10. *Huffman K.M., Kraus W.E. Osteoarthritis and the metabolic syndrome: more evidence that the etiology of OA is different in men and women. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2012; 20: 603-604.*
11. *Bredbenner T.L., Eliason T.D., Potter R.S., et al. Statistical shape modeling describes variation in tibia and femur surface geometry between Control and Incidence groups from the Osteoarthritis Initiative database. J Biomech. 2010; 43: 1780-1786.*
12. *Felson D.T., Lawrence R.C., Hochberg M.C., et al. Osteoarthritis: New insights - Part 2: Treatment approaches. Ann Intern Med. 2000; 133: 726-737.*
13. *de Klerk B.M., Willemsen S., Schiphof D., et al. Development of radiological knee osteoarthritis in patients with knee complaints. Annals of the Rheumatic Diseases. 2012; 71: 905-910.*
14. *Haverkamp D.J., Schiphof D., Bierma-Zeinstra S.M., et al. Variation in Joint Shape of Osteoarthritic Knees. Arthritis Rheum. 2011; 63: 3401-3407.*
15. *Neogi T., Bowes M.A., Niu J.B., et al. Magnetic Resonance Imaging-Based Three-Dimensional Bone Shape of the Knee Predicts Onset of Knee Osteoarthritis: Data From the Osteoarthritis Initiative. Arthritis Rheum. 2013; 65: 2048-2058.*
16. *Runhaar J v.M.M., Steens R, Vroegindeweij D, van Osch G, Reijman M, Koes B, Bierma-Zeinstra S Prevention of knee osteoarthritis in overweight females; from feasibility trial to full-scale trial. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2008; 16 (S141).*
17. *Altman R., Asch E., Bloch D., et al. Development of Criteria for the Classification and Reporting of Osteoarthritis - Classification of Osteoarthritis of the Knee. Arthritis Rheum. 1986; 29: 1039-1049.*
18. *Buckland-Wright J.C., Wolfe F., Ward R.J., et al. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: A comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol. 1999; 26: 2664-2674.*
19. *Kellgren J.H., Lawrence J.S. Radiological assessment of osteo-arthrosis. Annals of the Rheumatic Diseases. 1957; 16: 494-502.*
20. *Cootes T.F., Taylor C.J., Cooper D.H., et al. Active Shape Models - Their Training and Application. Comput Vis Image Und. 1995; 61: 38-59.*
21. *Mei L., Figl M., Rucckert D., et al. Sample Sufficiency and Number of Modes to Retain in Statistical Shape Modelling. Lect Notes Comput Sc. 2008; 5241: 425-433.*
22. *Runhaar J S.D., van Meer B, Reijman M, Bierma-Zeinstra S, Oei E How to define subregional osteoarthritis progression using semi-quantitative MRI Osteoarthritis Knee Score (MOAKS). Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2014; Inpress.*
23. *Hunter D.J., Guermazi A., Lo G.H., et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score) (vol 19, pg 990, 2011). Osteoarthr Cartilage. 2011; 19: 1168-1168.*
24. *Crema M.D., Roemer F.W., Felson D.T., et al. Factors Associated with Meniscal Extrusion in Knees with or at Risk for Osteoarthritis: The Multicenter Osteoarthritis Study. Radiology. 2012; 264: 494-503.*
25. *Berthiaume M.J., Raynauld J.P., Martel-Pelletier J., et al. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Annals of the Rheumatic Diseases. 2005; 64: 556-563.*
26. *Donnelly S., Hart D.J., Doyle D.V., et al. Spiking of the tibial tubercles--a radiological feature of osteoarthritis? Ann Rheum Dis. 1996; 55: 105-108.*
27. *Reiff D.B., Heron C.W., Stoker D.J. Spiking of the Tubercles of the Intercondylar Eminence of the Tibial Plateau in Osteoarthritis. Brit J Radiol. 1991; 64: 915-917.*
28. *Muneta T., Takakuda K., Yamamoto H. Intercondylar notch width and its relation to the configuration and cross-sectional area of the anterior cruciate ligament - A cadaveric knee study. Am J Sport Med. 1997; 25: 69-72.*
29. *van Eck C.F., Martins C.A., Lorenz S.G., et al. Assessment of correlation between knee notch width index and the three-dimensional notch volume. Knee Surg Sports Traumatol Arthrosc. 2010; 18: 1239-1244.*
30. *Kannus P., Jarvinen M. Posttraumatic Anterior Cruciate Ligament Insufficiency as a Cause of Osteo-Arthritis in a Knee-Joint. Clin Rheumatol. 1989; 8: 251-260.*
31. *Runhaar J. Prevention of knee osteoarthritis in overweight females; the first preventive randomized controlled trial in OA. In: Development and prevention of knee osteoarthritis: The load of obesity Rotterdam: Erasmus University Rotterdam 2013; 51-68.*
32. *Felson D.T. Does excess weight cause osteoarthritis and, if so, why? Annals of the Rheumatic Diseases. 1996; 55: 668-670.*

Valve-related outcomes in patients undergoing primary pulmonary valve replacement surgery with bioprostheses

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Introduction

Although the pulmonary valve is the least commonly replaced heart valve, it may require replacement either at primary repair of a congenital heart defect or at reoperation. Bioprostheses are the most widely used prosthesis type for pulmonary valve replacement (PVR), because they are readily available and do not require permanent anticoagulation therapy. However, most of these bioprostheses will eventually fail due to structural valve deterioration (SVD) and require replacement. Our aim was to perform an updated review of early and late mortality, reintervention and valve dysfunction rates in patients undergoing primary PVR surgery with bioprostheses.

Methods

We searched PubMed for English articles published between January 1st 2005 and January 1st 2015 on the long-term outcomes of bioprosthetic PVR. Data collection and statistical analyses were conducted according to the guidelines for reporting mortality and morbidity after cardiac valve interventions.

Results

Our PubMed search yielded 59 articles. We excluded 49 articles based on title, abstract or study design and 4 papers based on full text. Ross procedures, transcatheter and percutaneous PVR, and homografts were excluded. We eventually performed a quantitative analysis on 6 articles. The overall early mortality rate was 1.19%. The linearized occurrence rates of late mortality, reoperation and valve dysfunction ranged respectively between 0.18-0.97, 1.29-5.03 and 1.67-6.91% per year. Age less than 15 years appeared to be a risk factor for reduced freedom from reintervention (HR 95% CI: 0.85, p=0.004 and HR 95% CI: 0.86, p<0.001) and freedom from valve dysfunction (HR 95% CI: 0.86, p=0.009 and HR 95% CI: 0.85, p=0.001).

Conclusions

Primary bioprosthetic PVR can be performed with relatively low mortality rates. The valves remain fairly stable until 5 years after operation. Despite the relatively high valve dysfunction rates per year, reoperation rates remain low. As a secondary outcome, young age was significantly associated with reduced freedom from reintervention and increased valve dysfunction. This implies that patient age at surgery, regardless of valve type, primarily determines valve performance over time.

Table 1

Study	Follow-up (year)	Early mortality (%)	Late mortality (% per year)	Reoperation (% per year)	Follow-up (year)
Batlivala et al	3,20	0,59	0,18	1,29	6,07
	a.				
Chen et al	4,02	1,24	0,31	1,85	-
	a.				d.
Lee et al	7,30	1,66	0,53	3,25	1,67
	b.				c.
Fiore et al	2,16	1,49	0,67	2,76	6,91
	b.				
Kwak et al	3,00	0,97	0,97	2,59	-
	b.				d.
Belli et al	8,17	-	0,17	5,03	-
	a.		e.		

Primary outcomes. a) Mean b) Median c) Cases with reoperation and interventional balloon valvuloplasty were excluded in this study d) Not properly defined e) Only non-conduit-related late deaths.

Table 2. Young Age as a risk factor for valve-related events.

Study (Age at PVR in years)	Freedom from reintervention (HR 95% CI)	Freedom from valve dysfunction (HR 95% CI)	Reintervention (HR 95% CI)
Batlivala et al	0.84 (0.74–0.94)	0.86 (0.77–0.96)	-
(16.0 ± 3.3)	P=0.004	P=0.009	
Chen et al	-	-	19.54 (2.56–149.19) P=0.004
(< 15)			
Lee et al	0.86 (0.81–0.91)	0.85 (0.78–0.93)	-
(14.2 ± 9.8)	P<0.001	P=0.001	
Fiore et al	-	-	Patients who underwent
			reintervention were all less than
Kwak et al	-	-	15 years old.
			-
Belli et al	-	-	-

Extended Abstract

Immature granulocytes predict microbial infection and its adverse sequelae in the intensive care unit

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Background

About 50% of clinically suspected infections in the intensive care unit (ICU) can be confirmed by imaging techniques and microbiological cultures. As SIRS criteria also fail to successfully differentiate between an infection or other inflammatory illnesses, the need for a quick and sensitive diagnostic tool to detect infection is essential. Especially in the critically ill. We evaluated the predictive value of immature granulocyte (IG) percentage in comparison with white blood cell counts (WBC) and C-reactive protein (CRP), for infection, its invasiveness, and severity in critically ill patients.

Methods

In 46 consecutive patients, blood samples were collected at the day (0) of a clinical suspicion of microbial infection and at days 1 and 3 thereafter. We defined infections, bloodstream infection, and septic shock within 7 days after enrollment.

Results

Of the 46 patients, 31 patients had infection, 15 patients developed bloodstream infection, and 13 patients septic shock. C-reactive protein and IG percentage increased with increasing invasiveness and severity of infection, from day 0 onwards. Receiver operating characteristic analysis to predict infection showed an area under the curve of 0.66 (P = .10) for WBC vs 0.74 (P = .01) for CRP and 0.73 (P = .02) for IG percentage on day 0. Comparing WBC and CRP to WBC and IG percentage results in comparable prediction of microbial infection. Adding IG percentage to WBC and CRP gives an area under the curve of 0,80 (P=.01) for day 0, 0.87 (P=.01) for day 1 and 0.88 (P=.001) for day 3. The area under the curves for the combined test (Comparing WBC and CRP with WBC, CRP, and IG percentage suggests an additional early value of IG percentage, when not elevated, in ruling out infection.

Conclusions

Immature granulocyte percentage is a useful marker, as CRP, to predict infection, its invasiveness, and severity, in critically ill patients. However, the IG percentage adds to WBC and CRP in the early exclusion of infection and can be obtained routinely without extra blood sampling or costs.

Table 1 - Infection markers in patients with infection and BSI, patients with infection but no BSI, or patients without infection

	Day	Infection and BSI n = 15	Infection, no BSI n = 16	No infection n = 15	P
WBC,	0	9.6 (11.0)	12.6 (7.1)	8.9 (6.1)	.19
10^9/L	1	11.8 (4.8)	13.4 (7.9)	9.2 (5.5)	.02
	3	11.3 (9.2)	11.9 (7.7)	7.1 (2.9)	.02
CRP,	0	239 (247)	111 (67)	80 (65)	.008
mg/L	1	306 (152)	170 (168)	96 (114)	< .001
	3	245 (140)	106 (176)	89 (84)	.006
IG	0	1.3 (1.7)	0.4 (0.7)	0.2 (0.2)	.003
percen-	1	1.1 (2.4)	0.6 (0.8)	0.4 (0.6)	.006
tage	3	1.8 (2.7)	1.1 (1.5)	0.3 (1.1)	.009

Data are given as median (interquartile range).

The template for authors

Introduction

1. *What is the health-related problem that your research helps to solve?*

2. *What is your strategy to solve the problem?*

3. *What is your research question/hypothesis?*
   Whether a question or a hypothesis, state it in terms of 2 items:
   - variables: the measurable/observable independent and outcome variables that you measured/observed and
   - relationships: the relationships between those variables that your data analyses were designed to determine.

4. *The core concept of the methods you used to answer the research question*
   Briefly describe the core concept of the methods at the end of the Introduction section. This helps readers to understand the complex details that are then presented in the Methods section

Methods section

Organize the details of the Methods section under subheadings. Possible subheadings:

What was studied and study design (subheading)

Describe the details of
- what was studied: sample from a patient/animal population, and
- the design of the study: case-series, cohort study, case-control study, randomized trial, etc.

Data collection (subheading)

Describe the details of how the data was collected/observed

Note
Observable variables will be credible only if qualified observers and validated instruments were used to assess them. Examples of observable variables include patient symptoms, subject responses to open interviews/ questionnaires, ultrasound/MRI/CT images, assessments of articles in a literature review etc. In such cases, build credibility in the Methods section; report "who" observed and interpreted the data. For example, "An experienced radiologist interpreted the images."

Note
When reporting on decisions/judgments that were made, use the "we" form—take responsibility for what you did.

Note
The Methods section reports historical facts and must be in past tense.

Data analysis (subheading)

Results section

5. *The core concept of the Results*
   Briefly describe the core concept of the results in a short paragraph at the beginning of the Results section. This helps readers to understand the details that follow. Note just as in the Methods section, this section reports historical facts and must be in past tense.

Then organize the details of your Results under sub-headings, for example:

Patient/animal characteristics
Data
Statistical results

Discussion section

Structure your Discussion to focus on 4 core concepts (6, 7, 8, and 9 below).

6. *The answer to your research question*
   Present this right at the top of the Discussion section—the very first sentence, a present tense statement that expresses—to the best of your knowledge—how the world works as related to your research question/hypothesis. It is a direct answer to the question/hypothesis stated in the Introduction.
7. *Support that answer?*
   a) how your factual findings, (expressed in past tense), support your answer.
   b) relating the findings of others to your answer.
   c) theoretical considerations that support your answer.

Limitations (subheading)

8. *The limitations to that answer*
   Focus explicitly on limitations related to possible confounders:
   - sample size
   - specific locations/medical centers of your study,
   - possible ethnic/cultural variables,
   - uncontrolled patient/subject characteristics and
   - underlying assumptions.

Conclusions (subheading)

The Conclusion is not a summary, but should focus on the consequences of your work. Structure this subsection using separate paragraphs that state 2 main messages (9 and 10)

9. *What are the practical/theoretical consequences of your answer?*
   The value—relevance— of your work: how it helps to solve the problem described at the beginning of the Introduction.
10. *What is a next step to help solve the original problem?*
    - a new research question to be answered
    - a refinement of the present study to reduce limitations
    - a protocol to implement the findings in the clinic

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In the process of reviewing a paper, please refer to the following points:

- Your first step should be to evaluate your relationship with the authors. To ensure the credibility of the process, reviewers should not have a conflict of interest with the authors. If this is a case, the paper should be appointed to other reviewers. Please keep us informed whether conflict of interest is an issue for you as an appointed reviewer.
- Is this work relevant and interesting for EJM?
- Are the objectives appropriate and clearly stated?
- Are the data valid?
- Are the conclusions valid and properly supported?
- Is the already existing work described adequately?
- Paper structure/organization; is this logical?
- Does abstract clearly convey meaning of the paper?
- Is the paper well written and can be easily understood? (Please keep in mind that students don't have the experience to reed throughout the paper very quickly and to understand everything in a research paper at the first glance)
- Are all sections really needed, or could they be shortened?
- Is the science reliable? Please, be aware of ethical issues such as plagiarism!

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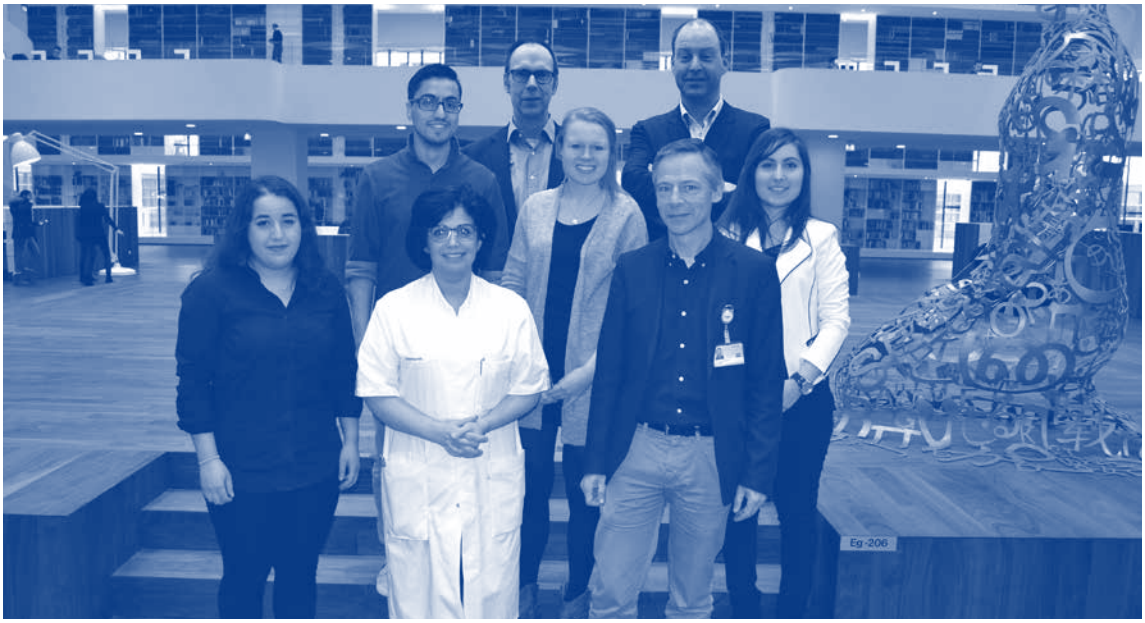

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