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The Digital Diet: Is Social Networking Mentally Healthy or not?

Seborrheic Keratosis: Can it be a Melanoma in Disguise?

Myth or Science? Spilling the Beans about Dietary Supplements

Lifestyle in Prevention of Cardiovascular Disease: What is the Role of Nitrate?

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Scientific articles have blue accents. Editorial articles have red accents.

FROM THE EDITORIAL BOARD

Dear readers,

This edition of RAMS will be the 14th edition and with a whole new board! We are excited to publish the upcoming RAMS editions this year! We aim to pursue the vision and mission of RAMS to enthuse our fellow students in the (bio)medical field. We hope we have combined the ability to ensure great learning and reading pleasure!

In this edition you will read about coeliac disease. We will tell you what is known and how you can spot this poorly recognised disease. Another topic is vitamins: are vitamins beneficial for your health or is it just a smart marketing trick? Also, we will discuss the effects of the usage of internet on your mental health. Nowadays, everyone knows how addictive social media can be. But is this a problem? Read all the answers in this edition.

The scientific article will discuss the literature regarding cardiovascular disease. Cardiovascular disease is the second main cause of death in the Netherlands. Besides traditional medication, could a Mediterranean diet, which is high in nitrates, lower the chance of cardiovascular disease? Subsequently, does the combination of high nitrate intake and proteins cause cancer and is thus not advised? Speaking of cancer: many people will develop seborrheic keratosis. Is that a melanoma in disguise? The current Zebras of Medicine in this edition will set out the clinical presentation, diagnosis and treatment of both skin alterations. Do you know how to make a distinction between these brown skin spots?

We hope you will have lots of learning and reading pleasure with this new edition of RAMS!

We would like to thank the editorial board of 2018/2019, Joyce Krekels, Maaike Plug and Naaz Shareef, for advising and providing feedback.

Yours faithfully,

Jelmer Raaijmakers, Scientific Editor-In-Chief

INDEX

THE DIGITAL DIET: IS SOCIAL NETWORKING MENTALLY HEALTHY OR NOT?

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Insights

In the last decade, the use of social networking sites (SNS) has grown exponentially worldwide [1]. In the United States of America, there has been a nearly tenfold increase in the usage of SNS platforms in the past ten years [1]. We went from a time where it was rare to have an internet connection at all to finding it weird when people do not have a smartphone or engage in social media. In a healthy 'digital diet', the use of SNS can have many positive outcomes, for instance increased perceived social support [1]. However, keeping the digital diet healthy has been proven to be a challenge to many people, speaking of terms such as 'digital detox', 'fear of missing out' and being 'alone together' [2, 3]. Also, a mounting body of evidence is suggesting associations between the use of SNS and mental health problems in adolescents [4]. Adolescence is a vulnerable period for the development of mental health problems such as depression and SNS addiction, because in this phase of life the development of identity, autonomy and social relationships is important, as are social support and fear of missing out. Mental health problems in this period indicate a higher risk of poor mental health for the rest of someone's life [4]. This editorial will give a brief overview of SNS usage on addiction and depression specifically, based on the latest scientific literature.

Introduction

Social networking sites (SNS) and social media are not the same [3]. However, the terms are often used interchangeably [3]. Social media refers to the web capabilities of producing, sharing and collaborating on content online [3]. SNS is described as web-based virtual communities in which it is possible to build a (semi-)public individual profile and articulate a list of other users to share a connection and to communicate with, for example Facebook and Instagram [1, 2]. In short, SNS are a type of social media. Other social media include collaborative projects like Wikipedia, weblogs like Youtube and virtual game worlds [3]. In this editorial, we will be focusing on the use of social networking sites in adolescence specifically. These online forums for communication are increasingly present in daily life, especially among teenagers and young adults [2]. As most readers know, Facebook is one of the most frequently used SNS, with around two billion users worldwide in 2016 [2]. This is the reason why present research on SNS is conducted mainly with Facebook.

Why do people use SNS?

Use of SNS is driven by a number of motivations. For instance, it could be the case that social networking meets the basic human needs like described in the hierarchy of needs by psychologist Maslow [5]. According to Maslow's theory, social networking meets the needs of safety, association, estimation and self-realisation [5]. The need of safety is met by the possibility of SNS to allow users to control whom they share information with [3]. The associative needs are accomplished by the connecting function of SNS with like-minded individuals [3]. The need of esteem is met through the gathering of friends and likes and comparing this to others [3]. Self-realisation can be reached by presenting oneself in the way one wants to present oneself [3].

In addition, a systematic review from 2012 proposed a dual-factor model of the use of Facebook [6]. According to this model, the use of Facebook is motivated by two basic social needs: the need to belong and the need for self-presentation [6]. The need to belong refers to the need to gain social acceptance and the need for self-presentation refers to the management of the impression you make on other people [6]. Humans are dependent on the social support of others and banishment from a social group has a negative impact on one's self-esteem, emotional well-being, one's sense of belonging and self-worth [6]. It has been proposed that a drop in self-esteem is a warning signal of potential social exclusion [6]. Some studies suggested that the use of Facebook is to some degree determined by cultural and sociodemographic factors, motivated by the fact that females and ethnic minorities tend to use Facebook more often than males and Caucasians [6]. In 2010, Gonzales *et al.* designed a study to examine if exposure to information presented on one's Facebook profile enhances self-esteem, especially when that person selectively presents or edits the information [7]. This suggests that digital self-presentation can alter self-assessment (the way one sees himself) [7]. Research showed that SNS are attractive to adolescents specifically because these websites enable them to construct a social identity through online profiles [8]. These profiles can be controlled, and thus teenagers are able to express their desired self-presentation [2, 6]. Adolescents can interact with others via these 'virtual selves' through a medium that is often unsupervised from adults [2]. Other positive effects of social networking are enlargement and management of social capital, connection with others and satisfaction of their need to belong in a technologically dominated society [6, 7, 9].

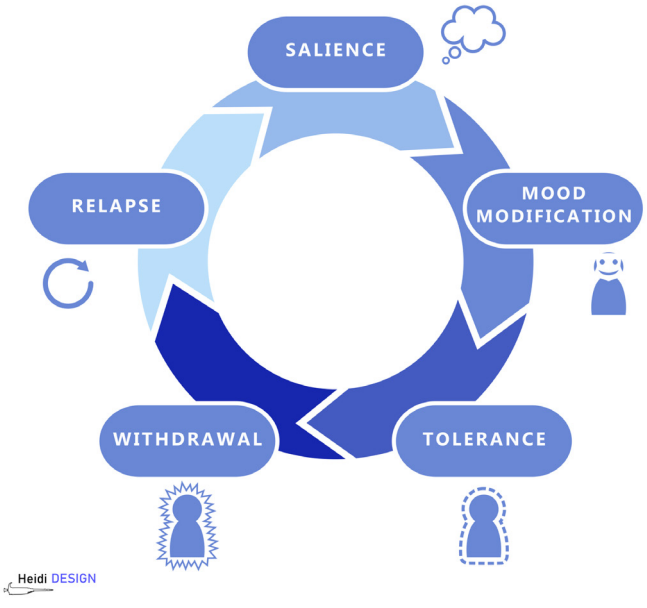

Figure 1: Key components of addiction.

SNS addiction

Besides the positive effects of SNS use, there is growing scientific evidence of an association between SNS use and poor mental health, ranging from binge drinking, phubbing (checking the smartphone in the middle of a face-to-face communicative situation), depression, social anxiety and addiction-like symptoms [1, 2, 4, 10]. Addiction to social networking sites is not officially recognised as a mental health disorder. However, it could be considered addictive behaviour, as it reflects key components from other addictive disorders (Figure 1) [1]. The global prevalence rate of people who feel such symptoms and meet addiction classification criteria is around six percent, which ranges from roughly eleven percent in the Middle East to around three percent in Northern and Western Europe [10]. Specific components of addiction are cognitive and behavioural salience, mood modification, tolerance, withdrawal, conflict and relapse [1, 3]. The process of getting addicted to SNS could be as follows: use of SNS dominates the thoughts and behaviour of the user (salience) [3]. The use of SNS then induces mood alterations, such as pleasurable or numbing feelings (mood modification) [3]. In order to achieve the same feelings that occurred in the initial phase of usage, increased amounts of time and energy are required in the SNS use (tolerance) [3]. When SNS use is discontinued, the user will experience negative emotions (withdrawal), which often lead to resuming the problematic behaviour (relapse) [3]. In terms of Facebook addiction, use of Facebook rewards the adolescent with positive reactions and feelings because it gives the sense of belonging they are so sensitive to. Because of the frequent Facebook use and the frequent rewards of the use, it becomes an automatic process that is stored in the brain as a reflex. Discontinuing this reflex requires suppression of this automatic process, which is only possible with conscious alternative behaviour that is also rewarding and positive.

Habit and reflection

Addiction symptoms develop when SNS use takes place compulsively in situations where it is better to not use SNS [10]. Compulsive use of SNS is automatic, irrational and temporary [10]. A model that explains the simultaneous rational and irrational processes is the dual-system theory of behaviour [10]. This theory describes that human behaviour is guided by both reflective and reflexive processes [10]. In the case of SNS use, the reflexive system is the manifestation of habit. In other words, the extent to which people tend to automatically use SNS [10]. This system is fast and automatically activated in response to cues like a message notification or a cell phone beep [10]. The reflective system, on the other hand, enables a person to perform reasoned actions that may override an automatic action already taking place [10]. This system is relatively slow [10]. When the impulsive system (habit) wins from the reflective system, addiction symptoms can emerge [10]. Research has shown that individuals that are able to reflect on their SNS use are also able to regulate their use [10]. Furthermore, they report less SNS addiction symptoms [10].

Fear of missing out

A concept that may contribute to SNS addiction is fear of missing out (FOMO) [3]. FOMO is defined as "a pervasive apprehension that others might be having rewarding experiences from which one is absent" and as "a desire to stay continually connected with what others are doing" [2]. Individuals worrying about not being able to connect to their networks may develop impulsive checking habits [3]. Furthermore, in adolescents with psychological problems like anxiety and depression, FOMO has a mediating role in the development of negative consequences of SNS use, as seen in Figure 2 [2]. Depression itself also has a direct effect on the negative consequences of SNS use [2]. Interestingly, the intensity of SNS use, the time spent on social networking sites, does not mediate the relationship between psychopathological symptoms and negative consequences of SNS use. The intensity of social networking is thus not the main risk factor for negative consequences, but it does mediate the effect of FOMO on the negative consequences [2]. Higher levels of FOMO are associated with more engagement with for example Facebook, lower general mood and wellbeing, lower life satisfaction, mixed feelings while using social media and inappropriate and dangerous SNS use such as checking Facebook while driving [2]. FOMO might be a component of potential SNS addiction [3]. Further research is needed to explore the origins of FOMO and into why some SNS users are prone to FOMO and addiction compared to users who are not [3].

Figure 2: Risk factors for negative consequences of SNS use.
Fear of missing out and depression have a direct effect on negative consequences. Depression also has an indirect effect on negative consequences, just like anxiety and social network intensity. Fear of missing out itself directly influences anxiety and social network intensity.

Nomophobia

Related to the fear of not being able to engage in social connections, and a preference for online social interaction is the phenomenon of nomophobia [3]. Nomophobia is derived from no mobile phone phobia, in other words, the fear of being without one's mobile phone [3, 11]. It can lead to using the mobile phone in an impulsive way and this may contribute to repeated use of SNS, which in turn can be a contributing factor to SNS addiction [3, 11].

SNS and mental health

It could be argued that the addictive-like symptoms in problematic users could be linked to psychological distress and also have a negative impact on general well-being [12]. For example, the mood modification and compulsive symptoms that emerge in SNS addiction might enhance the mechanisms involved in development of anxiety and depression [12].

It is well known that there is an increase in prevalence of depression in females during adolescence [2]. In 2011, the phenomenon of Facebook depression was first proposed, describing adolescents developing symptoms of depression after spending large amounts of time on SNS or high checking frequency of SNS [13, 14]. The term has gained popularity, but there is no consensus within the scientific community about it because the results of several systematic reviews attaining the topic are inconsistent [13]. A possible contributing factor to the Facebook depression is that SNS use might lead to wrong impressions of other users. People generally only share positive aspects about themselves on Facebook, resulting in comparing oneself with other users in a negative way [13]. From a psychological evolutionary perspective, people have a natural bias to individuals with higher levels of attractiveness and

status, because they can learn skills from them [13]. This bias towards the success of others increases the risk of negative self-talk and depression [13]. The results from a 2019 meta-analysis on SNS usage and depression supported that greater time spent on SNS and the SNS checking frequency were both associated with higher levels of depression. However, it seems that in some of the studies included in the analysis the relation between SNS usage and depression is stronger in some specific populations and contexts [13]. Further research is needed to establish the exact relationship [13]. A proposed mechanism of this relationship is the level of making social comparisons and consequently drawing false conclusions about other users' lives, resulting in a negative judgement of oneself and consequently depressed feelings [13]. However, more research into the exact mechanisms is needed.

Conclusion

SNS are the modern platforms for socialising, self-presentation and the sense of belonging, all important parts of development in adolescent life. However, adolescents are vulnerable to getting addicted and the increased use of SNS in adolescents raises questions about its effect on mental health. Addiction to social networking sites is not officially recognised as a mental health disorder, but addiction symptoms are prevalent globally. Parents commonly believe that the intensity of social networking is the sole risk factor for negative consequences for adolescents, but FOMO and nomophobia are possibly even more important factors. In conclusion, the digital diet of social networking seems to be mentally unhealthier than presumed by most people.

Acknowledgements

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EXAM QUESTIONS

As RAMS aims to enlighten both students and professionals, we would like to present you two exam questions. Find out if you can remember what you have learned during your bachelor's!

We challenge you!

Question 1

Some retroperitoneal organs still have a narrow relation with the peritoneum. Which organ does not cross the peritoneum at any point?

A. Sigmoid colon
B. Kidneys
C. Pancreas

(Topic from Q9 KVS, 2018)

Question 2

Some men have a higher than average risk of developing prostate cancer. The men with the highest risk are men with ...

A. A first-degree family member who has prostate cancer
B. Professional asbestos exposure in the past
C. A low cervical cross section

(Topic from Q10 KVS, 2018)

The answers to these questions can be found on page 13 in this journal.

MYTH OR SCIENCE?
SPILLING THE BEANS ABOUT DIETARY SUPPLEMENTS

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Critical Appraisal

Globally, more than two billion people suffer from at least one, persistent or periodic, micronutrient deficiency [1, 2]. Micronutrients are essential vitamins and minerals, required by the body in small amounts for proper growth and development, disease prevention and wellbeing. Examples of essential micronutrients are zinc, iron, iodine, calcium, vitamins A, B, and D [3]. In the Netherlands, 32.1% of men and 53.6% of women use one or more commercially available dietary supplement(s) containing (multi)vitamins, minerals or a combination of these two [4]. However, the necessity of these supplements in healthy adults remains questionable. Therefore, this article will answer the following question: do dietary supplements really improve your health or are they just a waste of money?

Introduction

All micronutrients must be derived from the diet; therefore, a balanced and varied diet is important. This includes sufficient intake of nuts, fruits, vegetables and whole grains [5, 6]. Also, plant-based foods, lean protein foods and low-fat dairy products are important to meet the Recommended Dietary Allowance (RDA), in µg/d or mg/d, for micronutrients [7].

The RDA is composed by gender and age category and is defined as the mean requirement for a micronutrient plus two times the standard deviation. Therefore, the RDA is a target value that meets the nutrient requirement of almost all healthy individuals [8-10]. However, the personal need of an individual will, in general, be lower than the RDA [9, 11-13]. However, some groups of people have a higher personal need for some micronutrients and, therefore, supplementary advices have been composed. These groups concern babies (vitamin D and when breastfed vitamin K), young children (vitamin D), women who want to become pregnant (folic acid) and during pregnancy (vitamin D and folic acid), elderly (vitamin D), people with dark skin or people who do not have enough sun exposure (vitamin D) and people who do not consume animal products (vitamin B12) [13].

Micronutrient deficiency

Micronutrient availability below the personal need over a longer period (months to years) may result in a deficiency. This process can have two causes: a primary or secondary deficiency [11, 12]. In case of a primary deficiency, micronutrient intake is insufficient due to, for example, a one-sided diet. A secondary deficiency means there is sufficient intake of micronutrients, but it is not available in the right form for the body, for example, due to malabsorption [11]. A secondary micronutrient deficiency is often related to an underlying disease. Regardless of the cause of the micronutrient deficiency, the body will run out of micronutrients. As a result, there will be less synthesis of metabolites and a decrease in the activity of vitamin-dependent enzymes and hormones [11]. This will eventually lead to biochemical and metabolic changes that are detectable in body fluids and tissue by biochemical techniques [11]. This is called a latent deficiency. If the deficiency is not restored, this phase can evolve into a manifest deficiency [11]. During a manifest deficiency, clinical observable, morphological and functional changes will occur, which may even lead to death [11]. For instance, a vitamin D deficiency is associated with impaired bone growth and myopathy [14, 15]. In addition, a deficiency in vitamin A, vitamin E, vitamin C, zinc and selenium might contribute to an impaired immunity and iron deficiency might result in iron deficiency anaemia [16-21]. These possible consequences of micronutrient deficiencies are summarised in Figure 1. In case of a deficiency, dietary supplements can be used to restore micronutrient availability in the body. However, as mentioned before, many healthy people are using dietary supplements as well, even though primary micronutrient deficiencies are rare in healthy adults living in Western countries [22, 11-13]. The most common reasons for using dietary supplements are the improvement of overall health and prevention of health problems [23]. However, a recent study in more than 27,000 adults found that there are beneficial associations with nutrients from foods that are not seen with supplements [24].

In addition, meta-analyses and systematic reviews of the past decade indicate no evidence for the use of dietary supplements for primary or secondary prevention of diseases like cardiovascular events, myocardial infarction, stroke, total death and cardiac death [25-28]. However, a supplement with possible positive health effects is folic acid [28, 29]. In 2015, a large Chinese randomised controlled trial reported that folic acid supplementation may reduce cardiovascular diseases (CVD), and specifically, stroke [28, 29]. Inclusion of this RCT in two recent meta-analysis of folic acid and CVD risk resulted in a 17% reduction in CVD risk and a 20% reduction in stroke [28, 29]. However, more research is needed on these supplements because the results are mainly based on this Chinese study. Therefore, there is no (hard) evidence that an intake of micronutrients above the personal need or RDA does have any additional, positive health effects in healthy adults [11-13, 25-29]. Furthermore, combined calcium plus vitamin D supplementation might increase the risk of stroke. Beta-carotene, vitamin E and high doses of vitamin A seem to increase early mortality [25, 30, 31]. Also, beta-carotene would increase the risk of lung cancer in (ex)smokers and people who worked with asbestos [30, 31].

Micronutrient excess

For different vitamins and minerals, a safe upper limit has been established; the tolerable upper intake level and intake should stay below this level. However, the dose of dietary supplements is often higher than the RDA [11, 32]. Therefore, the use of supplements might result in a micronutrient excess. Especially because supplement users already tend to have higher

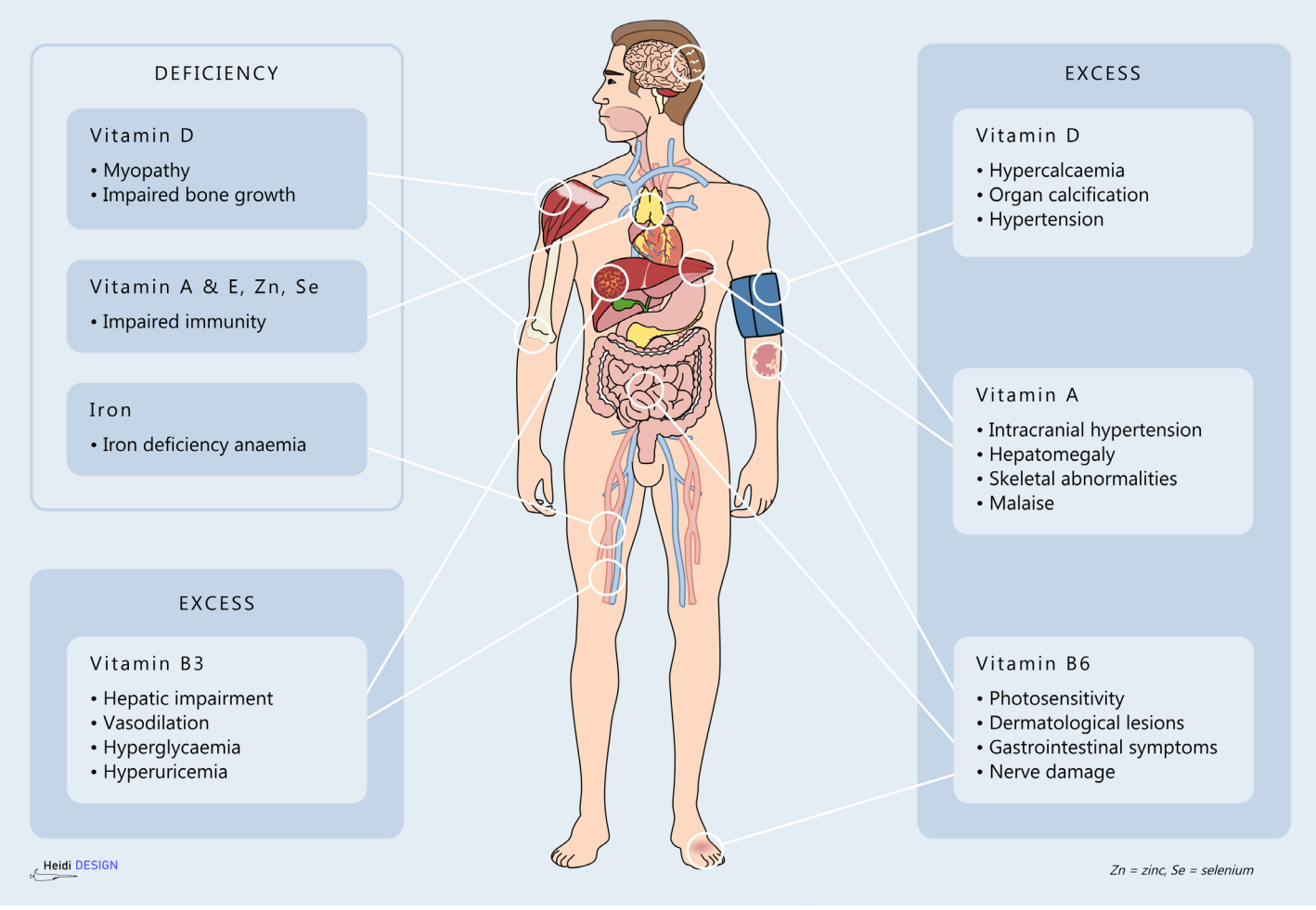

Figure 1: A summary of possible consequences of different micronutrient deficiencies and excesses.

nutrient intake from the diet itself [33-35]. This is probably due to the fact that supplement users have a higher nutrition awareness [35, 36]. As a result of micronutrient excess, micronutrient absorption in the intestinal tract will decrease and fat-soluble micronutrients will be stored in tissues and water-soluble micronutrients will be excreted in urine [11,13]. In addition, excessive intake of micronutrients might disrupt the normal metabolism or even reach toxic doses, which are associated with adverse health effects and deleterious consequences on health and development [11-13]. Especially, high doses of vitamin A, B3, B6 and D can be toxic [11, 37, 38].

A well-known example is the Dutch professional ice skater Sven Kramer, who suffered from nerve damage in his leg after a vitamin B6 excess due to dietary supplement use [32]. These dietary supplements contained 16 times the RDA for vitamin B6, which is equal to 25 mg [32]. Since October 2018, it is included in the Dutch Commodities Act that supplements may not contain more than 21 mg of vitamin B6 [39]. Nerve damage is the main toxicity of vitamin B6, but also gastrointestinal symptoms, photosensitivity and dermatological lesions might occur [37]. In 2014, the 'Gelderse Vallei' Hospital in Ede, the Netherlands, registered 300 vitamin B6 poisonings [32]. In addition, vitamin A excess might result in malaise, intracranial hypertension, hepatomegaly (an enlarged liver) and skeletal abnormalities [11, 38]. Besides, an excess of vitamin D might result in hypercalcaemia (high calcium levels), organ calcification and hypertension [11, 38]. Lastly, an excess of vitamin B3 might result in vasodilatation, hepatic impairment, hyperglycaemia (high blood sugar levels) and hyperuricemia (high uric acid blood levels) [11, 38]. Possible consequences of micronutrient excesses are summarised in Figure 1.

Conclusion

In conclusion, both micronutrient deficiencies and excesses can have negative health effects. However, a normal and varied diet in Western countries will contribute to sufficient intake of micronutrients. Therefore, dietary supplements should be used primarily in risk groups following the supplementary advice. Preventive dietary supplement use in healthy adults is not necessary. Although a multivitamin pill that does not exceed the tolerable upper intake level is a useful and safe supplement, the risk of excess should not be underestimated. If it turns out that you have a micronutrient deficiency, consider changing your diet before taking supplements.

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COELIAC DISEASE: AN UNDER-RECOGNISED DISORDER

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Perspectives

Patient A, a 56-year-old man, was admitted to the Department of Neurology because he had trouble walking in a straight line and was talking with slurred speech. He was diagnosed with cerebellar ataxia (poorly coordinated movements) of which the cause remained unknown after standard diagnostic workup [1]. During the time patient A was being evaluated, patient B, a 32-year-old woman, was admitted to the Department of Gynaecology because of a miscarriage. It was her third miscarriage that year and the cause could not be found [2]. While both patients were still in the dark about the cause of their symptoms, patient C, a four-year-old child, was seen by a paediatrician. Her mother was awfully worried because her daughter was suffering from chronic diarrhoea for the past year and was severely malnourished [3]. Although these three patients initially seem to have nothing in common, they actually share a lifelong illness. In the end, they were all diagnosed with coeliac disease [1, 2, 3].

Introduction

When the diet of humans changed from fruits, nuts and the occasional piece of meat to cultivated crops and various animals, new diseases arose. Novel antigens were introduced to mankind, which led to food intolerances. This new diet included antigens of cow milk protein, potatoes and gluten. This last protein is associated with coeliac disease (CD) [3]. Aretaeus of Cappadocia, a Greek physician of the first century AD, came up with the name. It is based on the Greek word "*koelia*" which means abdomen. Aretaeus called all individuals whose stomachs were unable to properly absorb food, coeliacs. In other words, coeliacs were all individuals who suffered from diarrhoea and malnutrition [4]. At the end of the 19th century, paediatricians Samuel Gee and Sidney Haas were able to link these symptoms to a specific diet. They published articles in which patients who suffered from CD were cured by a strict diet of Dutch mussels or bananas [5]. Although both were close to finding the culprit of this disease, the Dutch paediatrician Willem Dicke was the one who eventually figured out it was gluten in the year 1953. The discovery was made when professor Dicke found a paradoxical improvement in a subset of malnourished children in times of bread shortages during World War II. These children experienced a clinical decline and return of symptoms when Allied planes later dropped bread into the Netherlands [6]. His research is still considered revolutionary. Every five years, the golden Dicke-medallion is handed to gastrointestinal doctors with fundamental projects in the Netherlands [7].

In recent years, gluten intolerance has become a hype as many self-diagnosed individuals have embraced a gluten-free lifestyle. These individuals are not all "coeliacs" as the ancient Greeks would say [4]. They suffer from various symptoms ranging from fatigue to having a few extra pounds [8]. In the United States of America, one in five adults completely avoid gluten. For millennials, this percentage is even higher. Only one in twenty of these gluten-avoiders are actually suffering from CD [8]. Considering these statistics, one would assume CD has been overhyped in recent years. Conflicting enough, up to 90% of individuals who suffer from CD are still undiagnosed, making it a tremendously under-recognised disorder [9]. Since this disease can have many minor and severe consequences, it is a serious issue [9]. The widespread clinical presentation and the limited knowledge of healthcare providers may be the cause of underdiagnosis [10]. In this article, an extensive outline of CD is given with the aim to expand the readers' knowledge of this complicated disease.

Pathophysiology and aetiology of CD

Contrary to what most believe, CD is not an allergy, but an autoimmune disease with a very clear environmental trigger. Allergies are caused by the hypersensitivity of the immune system to harmless substances in the environment, whereas an autoimmune disease is an immune response to the body's own tissue [11, 12]. The environmental trigger for CD is gluten. Gluten is the main storage protein of wheat grains and consists of a mixture of hundreds of related but distinct proteins [13].

Gliadin (a digestive product of gluten) is thought to be directly and indirectly toxic to the cells of patients with CD [12, 13]. The human body forms both antibodies against gliadin and antibodies against the patient's own antigens, mainly tissue transglutaminase [12]. The forming of antibodies against the body's own antigens is the definition of an autoimmune disorder and the main pathway of disease in CD [11, 12]. The different pathways lead to an inflammation cascade which results in apoptosis (regulated cell death) and atrophy (loss of cells) of the intestinal wall of the patient [12]. In the small intestines, this means that villous atrophy occurs. The intestinal villi are small, finger-like projections that increase the internal surface area of the intestinal walls, resulting in a greater surface area available for absorption [12]. Therefore, loss of surface area causes malabsorption [12].

Classical and non-classical CD

The original CD population, as described by Dicke, mainly consisted of children with both symptoms of maldigestion and diarrhoea [6]. Maldigestion often leads to malnutrition, which causes insufficient weight gain in children or inappropriate weight loss, known as failure to thrive. Diarrhoea in patients with CD is often foul-smelling and greasy due to an excess of fat. This fatty diarrhoea is called steatorrhoea [14]. These symptoms are caused by the inability of the small intestines to break down and take up nutrition, including fat, due to the villous atrophy [12].

In the past few decades we have learned that CD is most often not as classic as once thought. Only six percent of all individuals with CD resemble the original paediatric patients [15]. The World Gastroenterology Organisation therefore distinguishes two forms of

CD: The 'classical' and 'non-classical' CD. As suggested by the name, the 94% of CD patients in the latter group have extremely heterogeneous symptoms, including less specific gastrointestinal (GI) symptoms, such as abdominal pain and altered bowel habits, and extraintestinal symptoms, which will be discussed in the next paragraph [15]. Unlike 'classical' CD, which presents at young age, patients with 'non-classical' CD most often develop symptoms in their fourth or fifth decade. It is therefore also described as adult CD [15]. The discovery of these non-classical CD patients made it a relatively common disease, affecting one percent of the population [17].

Extraintestinal symptoms of CD

As mentioned in the last paragraph, patients with non-classical CD have heterogeneous symptoms which are not limited to the gastrointestinal tract. This is because CD is actually a multisystemic disease, to which more than a hundred different symptoms are linked from various organ systems. [16].

About 50% of CD patients present with extraintestinal symptoms that can be divided into neuropsychiatric symptoms and other extraintestinal symptoms [18]. The most characteristic example of extraintestinal CD is dermatitis herpetiformis (DH). This blistering skin disease is characterised by an intense itching and burning rash on the extremities. This disease is exclusively caused by a gluten-sensitive enteropathy, even though DH patients often do not have GI symptoms [19].

The most frequent extraintestinal presentation of CD is anaemia. This appears to be mainly due to iron deficiency, since iron is absorbed in the proximal duodenum. The prevalence of CD in patients with iron deficiency anaemia is believed to be six percent for individuals without gastrointestinal symptoms and up to fifteen percent for patients who do have these symptoms [20]. Therefore, anaemia guidelines recommend to screen for CD, but there are still many individuals who are treated in vain with iron tablets [21]. Other deficiency syndromes, such as fat-soluble vitamin deficiencies, can also be the first and only symptom of CD [22].

Extraintestinal presentations of CD also includes disorders in fertility and pregnancy. Untreated CD is linked to significantly delayed puberty in both genders, earlier menopause and an increased prevalence of secondary amenorrhea (no menstruation for at least three months) [23]. Females with CD can also have an increased risk of miscarriage [23]. In males with CD the sperm quality may be reduced [23].

Another important category of symptoms associated with CD are neuropsychiatric disorders [24, 25]. Over 50% of patients with CD are affected by or develop peripheral neuropathy [24]. Other associated neurological symptoms are: ataxia, seizure disorder, migraine and dementia [24]. Depression and anxiety are examples of psychiatric disorders often linked to CD, as an appropriate treatment of the underlying CD can resolve these symptoms [25]. In Figure 1 the different categories of CD patients are displayed.

As opposed to GI-symptoms, the aetiology of these extraintestinal symptoms remains unclear in most cases. Some CD-associated symptoms share an immune-mediated aetiology. DH is for example known to be an autoimmune disease, thought to be caused by the same autoantigen as CD, called tissue transglutaminase. Certain neuropsychiatric symptoms are also thought to be caused by this autoantigen, as mouse models have shown that tissue transglutaminase antibodies cause ataxia-like deficits [26]. Other CD-associated symptoms are caused by micronutrient malabsorption, such as anaemia. However, it is likely that other elements are also involved [19, 27].

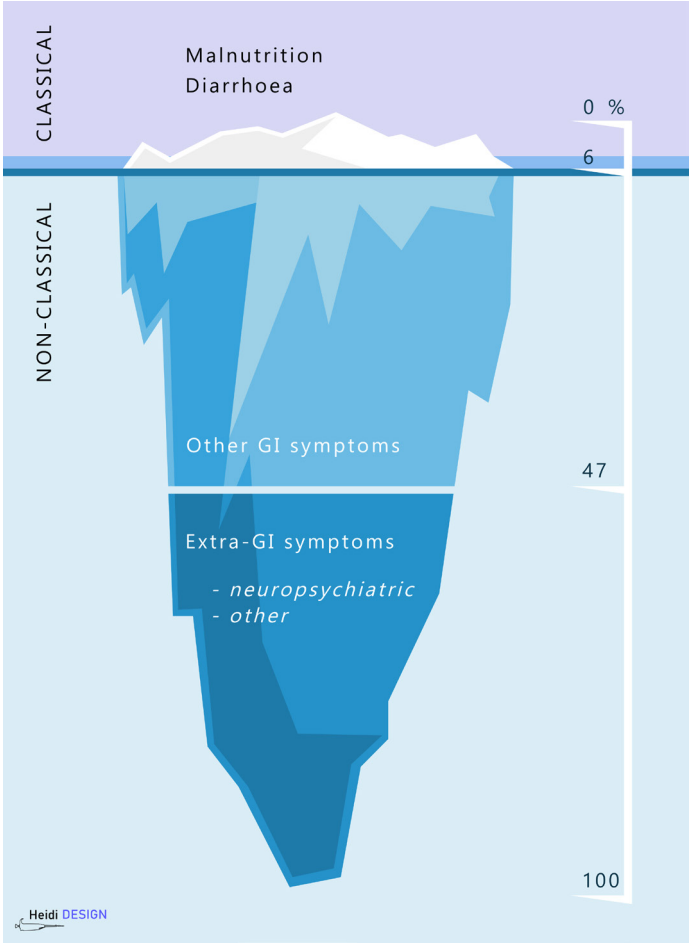

Figure 1: Presenting symptoms of coeliac disease (CD).
This figure illustrates that only six percent of individuals with CD present with the classic symptoms linked to this disease, which are malnutrition and diarrhoea. The other 94% of individuals with CD present with other symptoms, of which 50% is also gastrointestinal. The other 50% consists of extraintestinal symptoms, which can be divided into neuropsychiatric symptoms and various other symptoms.

Diagnosis

As mentioned before, up to 90% of individuals with CD remain undiagnosed [18]. Diagnosing CD is a challenging process that differs in local guidelines [29, 30]. When it comes to diagnosis of CD there are two main groups of patients, those with clinical symptoms of CD and those without symptoms, but a positive family history [18, 29]. Firstly, the patients are screened using serological or genetical testing (see Box 1) [29]. Secondly, the diagnosis is affirmed, by analysing endoscopically retrieved biopsies matching CD under a microscope. This is invasive for patients [29]. Screening is advised by the Coeliac Disease Foundation for all individuals older than three with symptoms of CD, first-degree relatives of patients with CD and any individual with an associated autoimmune disorder. The options regarding screening consist of multiple serological and genetic tests.

Because of shortcomings of both serological and genetic testing, a biopsy of the small intestine is the only way to confirm the diagnosis, even though this does require invasive diagnostic testing. Samples are collected from the duodenal wall for pathological testing using gastroduodenal endoscopy [29] .

Patients' resistance to gastroduodenal endoscopy, age or difficulty screening due to gluten-free diet requires the physicians to be flexible

Serology [18, 29-31]
The tissue transglutaminase IgA antibody and IgA antibody test (tTG-IgA test) is the first step in testing for CD for those who are eating a gluten-containing diet. The tTG-IgA test has a sensitivity of 98% and a specificity of 95%. Total IgA antibodies are tested to rule out that a patient is IgA-deficient, rendering the tTG-IgA test unreliable.

Other serological tests include IgA and IgE endomysial antibody and deamidated gliadin peptide (IgA and IgG). While these are being used for testing individuals with low IgA antibody levels and to double-check for potential false positives or false negatives. They do not offer much in making final diagnoses as sensitivity and specificity are low, and due to this double false negative or double false positive testing is still possible. Furthermore, a single negative serological screening is not enough to rule out CD later in life, as the disease can develop after prolonged exposure to gluten.

Genetics [18, 29, 30]
Genetic testing is based on testing for the *HLA DQ2* and *DQ8* genes. Testing negative for both these genes excludes the possibility of having or developing CD. This is irrespective of gluten-containing diet and age. The genetic testing cannot be used to diagnose CD because if you carry *HLA DQ2* and/or *DQ8*, your risk of developing CD is still "only" three percent. Up to 30% of the population tests positive for these genes. However, with a negative test for the *HLA DQ2* and *DQ8* genes, CD can be excluded, making the test a viable option for screening patients with family members with CD.

Box 1: In-depth information about serology and genetics in CD.

with diagnosing CD. It sometimes results in using an improvement due to a gluten-free diet (GFD) as a diagnostic tool. However, this introduces false positive diagnosis due to the placebo effect [29]. Recent evidence suggests that endoscopy is not obliged if clinical presentation and serological testing align, making the diagnosis very likely [30, 32].

Treatment

Currently, the only treatment of CD is the lifelong adherence to a GFD [33]. However, over half of patients with CD do not achieve an excellent or good level of adherence. Patients explain that the diet is psychologically and practically challenging, as many foods contain gluten and gluten free food is more expensive [34]. A recent study found that the of burden of following a GFD is comparable to that of dialysis in end-stage renal disease [35].

Around 30 to 50% of patients do not respond well to this treatment, often due to diet mistakes [36]. There is also a small group of patients who do not respond to treatment, even when the GFD is precisely followed. This is called non-responsive CD or refractory CD and it is defined as persisting symptoms of CD, elevated CD antibodies or small intestinal damage (seen during endoscopy) after following a strict GFD for 6 to 12 months. It is important to properly check the diets of non-responsive patients and to exclude alternative diagnoses that could have caused the symptoms to be falsely linked to CD [29, 36].

Since a GFD is hard to follow for various reasons and not all patients respond well to it, newer therapeutic modalities are being studied in clinical trials. An example is an antibody fragment that blocks the invading gluten molecule without triggering the immune system [37]. However, this is still in an experimental stage, therefore, at this moment CD patients still have to follow a GFD.

Conclusion

CD is a common disorder, since it affects one percent of the population. The classical presentation of this disease is maldigestion and diarrhoea, which starts at a young age. However, over 90% of patients present with different symptoms and at various ages. These symptoms consist of less specific gastrointestinal symptoms, such as abdominal pain. In addition, they consist of more than a 100 extraintestinal symptoms, such as DH, anaemia, fertility problems and certain neuropsychiatric disorders. This heterogeneity in presentation explains why up to 96% of individuals with CD remain undiagnosed, making it a tremendously under-recognised disorder. Since CD has a major impact on the quality of life, it is important that doctors become more aware of the fact that CD is a multisystemic disease with a broad variety in presentation and of the diagnostic and treatment options of this disorder as outlined in this article.

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
B. Kidneys

The dorsal side of the kidneys is adjacent to the dorsal abdominal wall. The anterior side has contact to several other organs. Together with the adrenal glands, the kidneys are separated from the other abdominal organs by the parietal peritoneum, the renal fascia and the adipose capsule.

For further reading:
Waschke, P. *Pelvis and Retroperitoneal Space* in Sobotta: Atlas of Human Anatomy, Vol. 15 (Elsevier GmbH, Germany, 2011)

During the exam, 68% of the participants answered this question correctly.

Answer question 2:
A. A first-degree family member who has prostate cancer

Risk factors for prostate cancer include advanced age, race and a family history. The first-degree relatives of men with prostate cancer have twice the risk compared to the general population. This is higher than in those diagnosed below the age of 60 years and 50% higher in monozygotic twins.

For further reading:
Yaqoob, M.M. *Kidney and urinary tract disease* in Kumar and Clark's Clinical Medicine, Vol. 9 (Elsevier Ltd, the Netherlands, 2017)

During the exam, 73% of the participants answered this question correctly.
The exam questions can be found back on page 6 in this journal.

Assembly of the clinical issues (KVS) exam

The KVS exam is assembled by the KVS-committee, where many medical specialties are represented. This committee gathers once every two weeks, and during these meetings, new questions (provided by all module coordinators) are evaluated in their appropriateness for the exam. After the exam is made by students, this committee looks extensively to the exam analysis and comments of the students. From this evaluation, it is decided what happens with these questions. Recently, the committee decided that a reaction to the student's commentary will be made available to read for all students. The final grading is then determined based on the Cohen-Schotanus formula, after which the final grades will be checked again and made public within 15 working days after the exam date.

ZEBRAS OF MEDICINE

SEBORRHEIC KERATOSIS: CAN IT BE A MELANOMA IN DISGUISE?

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Abstract

Review

Background: Seborrheic keratosis (SK), a raised black or brown papillomatous papule or plaque on the skin, is the most common benign skin tumour [1]. Over 80% of people over the age of 50 years have this type of skin tumour [1]. Its clinical presentation develops in later stages of life and can sometimes show similarities with a malignant melanoma. It is of crucial importance to detect melanoma in an early stage to prevent its dangerous progression.

Objective: This review compares SK with malignant melanomas in terms of clinical presentation, diagnosis and treatment.

Clinical presentation: If not well trained, SK and melanoma might look similar in terms of clinical presentation. However, the latter is a malignant condition in contrast to the benign SK. SK is generally a small, well-circumscribed lesion. Melanomas can be characterised by the ABCDE acronym. This acronym stands for (A)symmetry, (B)order irregularity, (C)olour variation, (D)iameter and (E)volving. In order to differentiate SK and malignant melanoma, mainly clinical criteria are used. SK does not necessarily need a treatment due to its benign nature [1]. The treatment of malignant melanoma is much more complex in comparison to SK due to the health consequences, severity of disease and differences in responding tumours [2]. The treatment of localised disease (stage I-III) consists of wide excision of primary tumours (*in situ*) with corresponding safety margins, which depend on the Breslow thickness [2]. Chemotherapy, or sometimes radiotherapy, might be applied if the tumour has metastasised.

Conclusion: Early detection of malignant melanoma is crucial, due to the clinical implications and disease severity. Melanomas can sometimes look clinically similar to SK, where the presence of a pigment network is the most important difference to suspect melanoma. SK does not necessarily need treatment. For physicians, it remains of utmost importance to critically inspect the lesion. Treatment of malignant melanoma varies widely and is tailored according to the stage of the melanoma.

KEYWORDS: Skin tumour, skin disease, chemotherapy, dermatology

Introduction

Dermatologists inspect suspicious looking skin lesions on a daily basis. While ageing, most of us develop darkened spots on their skin or even raised plaques. Seborrheic keratosis (SK) is a raised black or brown papillomatous papule or plaque and is the most common benign skin tumour [1]. This is present in 80% to 100% of people over the age of 50 years [1]. Due to its clinical presentation and the development in later stages of life, it can be suspected to be a melanoma. However, melanomas may also present themselves early in life.

A century ago, malignant melanoma was a very rare type of skin cancer [3]. However, the incidence of melanoma skin cancer is increasing and the lifetime risk of developing malignant melanoma has reached one in fifty persons on average [3]. It has become the fifth (for men) or sixth (for women) most frequent type of cancer. While SK is benign and harmless, melanomas are malignant skin tumours which lead to death. This review sets out to compare SK with malignant melanomas in terms of clinical presentation, diagnosis and treatment.

Clinical presentation

One of the differential diagnoses for SK is malignant melanoma [1]. SK presents itself as a raised, generally small, well-circumscribed plaque or papule that can look like a wart. The colour of the lesion can vary from reddish to brownish and the size ranges from a few millimetre up to a centimetre [1, 4]. SK presents itself frequently on the head and neck as just a single lesion, but a group of lesions may also appear. The lesions might show an irregular pattern or become irritated, and thereby mimic a malignancy [4]. Naevi, and therefore melanomas, can be characterised by the ABCDE acronym. This acronym stands for (A)symmetry, (B)order irregularity, (C) olour variation, (D)iameter and (E)volving. The latter was added for the diagnosis of nodular melanomas [3]. The criteria of the acronym can be seen as a checklist for naevi suspected to be a melanoma. There is a wide variety of clinical presentation for both SK and melanomas. This might make it hard for the untrained eye to certainly diagnose SK and melanoma. The following paragraph describes the diagnosis of either one of the tumours.

Diagnosis

Mainly clinical criteria are used to diagnose SK and malignant melanoma. SK diagnosis is based on the appearance and specific features of the lesion and the location, of which a pigment network is the most important distinction. Dermatoscopic features of SK are milia-like cysts and comedo-like openings [1]. Milia-like cysts (horn pearls) are round, white to yellowish structures and are not specific for SK, but is frequently seen [1]. Furthermore, the comedo-like openings (crypts), are brownish holes in the surface of the SK [1]. Lastly, the dermoscopic criteria include a brain-like appearance. Another way of diagnosis is taking a biopsy and confirm the diagnosis by means of histology [1]. This can be useful when lesions are itchy or bleed, are inflamed or changed into a dark colour [1]. It is important to note that if a melanoma is suspected, one should perform a diagnostic excision instead of a biopsy.

Just like SK, malignant melanomas are diagnosed using clinical features. Skin self examination has been of importance, since early discovered melanomas are mostly easily treated. Therefore, in 1985 the ABCDE acronym was established. The sensitivity of self skin examination is between 57%

Table 1: Overview SK treatments and their indication.

	1st treatment	2nd treatment	3rd treatment
Raised SK	Curettage or cautery	-	
Flat SK	Cryotherapy	Curettage	Laser, dermabrasion, chemical peel

and 90% [3]. Another tool that has been developed for early detection is the Glasgow 7-point checklist. This checklist contains three major criteria (evolving size, shape and colour), and four minor criteria (change in sensation, diameter greater than 7 mm, inflammation and crusting or bleeding) [3]. Since this checklist is more complex, it is not widely adopted. Dermoscopy is especially important for early diagnosis. This technique uses optic magnification to highlight features cannot be seen with the naked eye. Dermatologists then look at seven criteria: (1) atypical pigment network, (2) irregular dots/globules, (3) irregular streaks, (4) irregular pigmentation, (5) regression structure, (6) blue-whitish veil and (7) vascular patterns [3]. The final discussed method for diagnosis of melanoma is reflectance confocal microscopy [3]. This is a non-invasive examination of the skin that uses near-infrared light that passes through the upper layers of the skin [3]. The reflected light is captured and an almost histologic resolution can be reached. However, this is not done in daily clinical practice.

The guidelines, as presented by the European Society for Medical Oncology, state that complete diagnosis of melanoma should be based on a diagnostic excision, with a minimal side margin of 2 mm [2]. In higher stages (III-IV, when metastasis occur) mutation testing is mandatory in order to detect mutations that are targets for personalised treatment (e.g. *BRAF* mutations), whereas testing primary tumours for mutations is not recommended [2]. Staging and mutational testing is necessary in order to define the optimal treatment with the highest survival outcomes. In the following paragraphs, considerations are described regarding treatment options of melanoma. The tumour stages IIIB and IIIC (the letter depends on the tumour number of lymph nodes involved, whether it has satellite or in-transit lesions, and if it appears ulcerated), a complete image investigation of chest, abdomen and pelvis should be performed.

Treatment

It is not necessary to treat SK due to its benign nature [1]. If the SK becomes irritated, uncomfortable or itching, it can be removed by several forms of treatment [1]. Table 1 depicts an overview of the different treatments and their indication. People who started the treatment have a high chance to see good results [1].

The treatment of malignant melanoma is much more complex in comparison to SK due to the health consequences, severity of disease and differences in responding tumours [2]. The treatment of localised disease (stage I-III) consists of wide excision of the primary tumour (*in situ*) with corresponding safety margins [2]. The size of the excision is guided by the Breslow thickness (measure of how deeply a melanoma has grown into the skin) of the melanoma. A sentinel lymph node biopsy for precise staging is recommended for tumours with a thickness less than 0.8 mm with ulceration or between 0.8 and 1 mm with or without ulceration. Also, a sentinel lymph node biopsy should be taken if ulceration is present [2]. Patients with resected stage III melanoma should be evaluated for adjuvant interferon therapy (immune therapy that uses natural glycoproteins that are produced by cells of the immune system) [2]. As a therapeutic option, surgical removal and irradiation of locoregional recurrence or single distant metastasis should be considered. This has the potential for long-term disease control [2].

Following the guidelines of the European Society for Medical Oncology, if a patient has metastatic melanoma, the metastasis or the primary tumour should be screened for a specific mutation (*BRAF-V600*) [2]. This enables the treatment options of first-and second line setting. This includes anti-PD-1 antibodies and anti-CTLA4 antibodies [2]. BRAF/MEK inhibitor combinations can also be utilised for patients with a *BRAF*-mutant melanoma. If these medicines are not accessible, the cytotoxic DTIC (dacarbazine) or temozolomide may be administered, with limited efficacy [2].

Conclusion

Early identification of melanoma is crucial due the clinical implications and severity of disease of malignant melanomas. Because of the sometimes similar presentation, physicians need to remain critical when evaluating a lesion. SK is easily treated and treatment is usually not necessary. On the other hand, early diagnosis and staging of malignant melanoma is crucial. Treatment of malignant melanoma varies widely and is tailored according to the stage of the melanoma.

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LIFESTYLE IN PREVENTION OF CARDIOVASCULAR DISEASE: WHAT IS THE ROLE OF NITRATE?

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Abstract

Review

Background: Cardiovascular disease (CVD) remains a common cause of death in the Netherlands. Risk factors for CVD include smoking, obesity, hypertension, high cholesterol and physical inactivity. Currently, prevention and treatment of CVD is based on changing lifestyle and/or the use of medication.

Objective: In this review we will first identify the current practice regarding prevention and treatment of CVD and after that it will further elaborate on the influence of diet on the blood pressure (BP).

Results: Two components are identified in the current approach for the prevention of CVD in the Netherlands: medicated and non-medicated interventions. Both reduce the risk of developing CVD in both people with or without previous CVD. However, medicated interventions can have their side effects. Lately, several studies have explored the effect of dietary nitrate supplementation on the BP. Results from these studies suggest that dietary nitrate intake can lower both systolic and diastolic BP in hypertensive and normotensive subjects. This tension-lowering effect of nitrate is found to be due to its conversion to nitric oxide (NO) via the nitrate-nitrite-NO pathway.

Conclusion: Lifestyle interventions may be a good alternative to medication and even a conceivable way to prevent CVD disease progression. Although only the short-term effects are studied, dietary nitrate could be considered as a promising new lifestyle intervention targeting hypertension, thereby lowering the risk of several diseases, such as CVD.

KEYWORDS: Non-medical, treatment, diet, nitric oxide

Introduction

Almost 25% of total deaths in 2017 is caused by cardiovascular disease (CVD) in the Netherlands [1]. Additionally, 12% of healthcare costs were spent on CVD in the Netherlands in 2015 [2]. Thus, CVD is a threat to the health of many people. Therefore, multiple studies investigated why the incidence of CVD is so high and how this can be prevented or treated. A significant portion of these studies focused on the influence of lifestyle on CVD development and risk. According to the Dutch General Practitioners Society (NHG), there are a few risk factors for developing atherosclerotic plaques, known to be smoking, obesity, hypertension, high cholesterol and physical inactivity [3]. In 2015, diabetes and male gender were listed as additional risk factors [4]. Apart from diabetes and male gender, which are fixed factors, all the other risk factors can be altered. Within this review we will describe the traditional approach to treating and preventing CVD. After that, the focus will be on the influence of the diet on blood pressure (BP), an important risk factor for CVD.

Current treatment and prevention of CVD

In the Netherlands, the prevention of CVD includes two main components. The first main component of CVD prevention is medication. The NHG guideline focuses on two factors, being lipids and BP [3]. For lipids, LDL-cholesterol (LDL-C) is the most important risk factor. According to the guideline, the target value for LDL-C should be less than 2.6 mmol/l for people with a high risk of CVD and the target value is even lower (less than 1.8 mmol/l) for people who have already undergone CVD and need to prevent another cardiovascular event [3]. In the United States of America, the same values are included in the Adult Treatment Panel III of the National Cholesterol Education Program [5]. However, a meta-analysis from 2010 suggests that further lowering of LDL-C would yield additional benefits, without an increased risk on side effects [6]. Statins are the most used and most extensively studied cholesterol-lowering drug. A large meta-analysis from April 2019 concluded that statins are effective in preventing cardiovascular events in primary prevention, with atorvastatin being the most effective and safest [7].

The second important component in CVD prevention are non-medicated interventions, which are pieces of advice for the patients to improve their lifestyle in order to minimise the risk of CVD. Reduction of stress, depression and anxiety disorders; 150 minutes of moderate intensity exercise per week; quitting smoking; getting or keeping a healthy weight and eating healthy are listed in the NHG guideline as interventions to improve the risk factors [3].

Hypertension as risk factor for CVD

The development of CVD is a complex interplay of interconnected factors. Hypertension is one of the risk factors for CVD, but most of the other risk factors are at the same time also risk factors for hypertension. Lowering the BP can be done in multiple ways. Consistent with the 2016 European Guidelines on cardiovascular disease prevention in clinical practice, the lifestyle changes that are mentioned, are recommended for patients with an increased risk of CVD [8]. When the risk of CVD is high, hypertension should be treated according to the Dutch guideline [3]. Currently, the target value should be set at a systolic blood pressure (SBP) lower than 140 mmHg [3]. Diuretics, β-blockers, calcium antagonists, ACE-inhibitors and angiotensin receptor blockers are all effective BP-lowering drugs and can be combined if one drug on its own does not yield the desired drop in BP [9]. This also prevents dose-related side effects.

Besides medication, hypertension can also be tackled by changing lifestyle factors. According to a study by El-Atat *et al.*, obesity control might eradicate 48% of hypertension in the Caucasian population [10]. Huang *et al.* also showed a 26% decrease in the incidence of hypertension associated

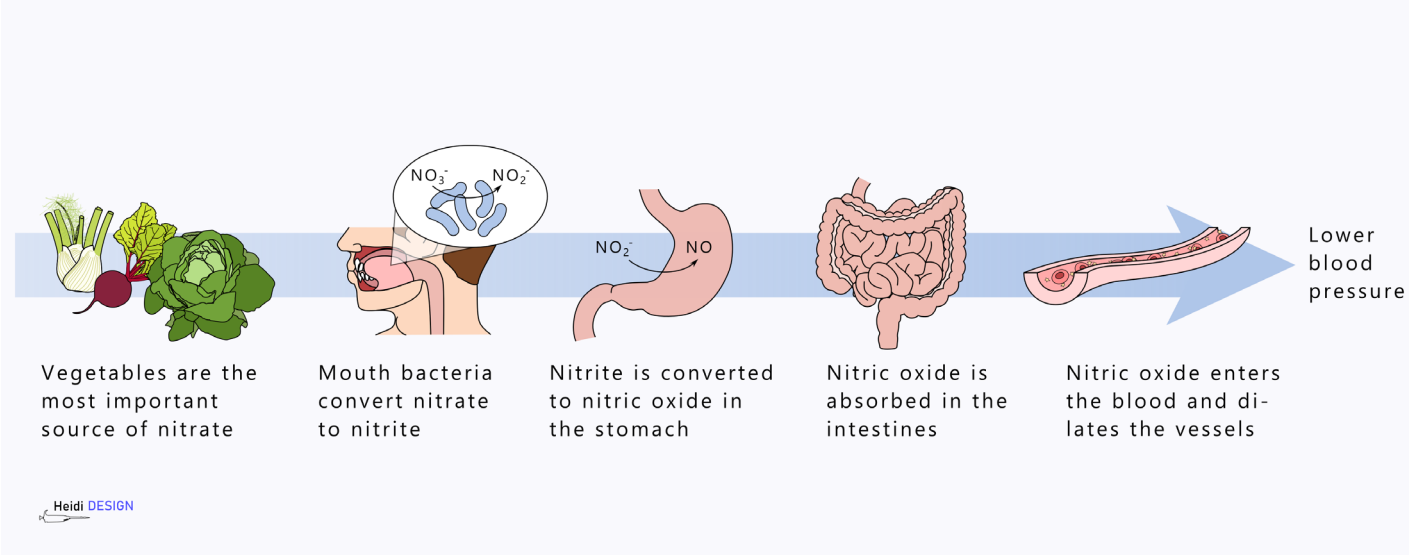

Figure 1: The path nitrate takes in the body and the effect it has on the blood pressure.

with long-term weight loss of 10 kg or more [11]. Accordingly, Becque *et al.* showed that 80% of obese adolescents indeed had an elevated BP [12]. Moreover, a meta-analysis from 2013 found that reducing salt intake to 4.4 grams per day leads to a significant drop in BP [13]. In the Netherlands, the recommended daily salt intake is currently set at a maximum of 6 grams per day [3]. Although this is beneficial to the BP, it is not ideal. According to Samadian *et al.*, it would be even better for the risk of hypertension to lower it even more to a maximum of 4 grams per day like in the United States of America [14].

The diet: a promising new way to influence the BP

The Seven Countries study was the first to show that the risk of CVD could be altered by diet. This study identified an association between a low incidence of CVD and the Mediterranean Diet, a diet low in dairy products and meat and rich in fruit [15, 16]. Additionally, the Dietary Approaches to Stop Hypertension diet, a diet focusing on vegetables, fruits, lean meats and whole grains, also showed beneficial effects on BP [17, 18]. Later on, the protective effects of both diets on cardiovascular parameters were found to be partially due to the high nitrate and nitrite content [19-21]. More precisely, recent research has suggested that vegetables with a high nitrate content are the most protective against CVD [20-25]. Prominent dietary sources of nitrate are water and vegetables, with vegetables being the main source of dietary nitrate in humans, contributing up to 80% of the total nitrate intake [26]. Rocket, spinach and beetroot are examples of vegetables that are rich in nitrate (more than 2,500 mg/kg), whereas for example mushrooms and onions have a very low nitrate content (less than 200 mg/kg) [27, 28].

Lately, dietary nitrate as a promising new nutrient has gained rising interest. Numerous studies have already explored the effect of dietary nitrate supplementation on BP. In these studies, BP was found to be reduced after nitrate supplementation both acutely (ranging from 1 to 24 hours), as well as short term (ranging from 3 to 21 days) [29-43]. A review of Siervo *et al.* found that nitrate supplementation lowered systolic and diastolic BP up to 4.4 mmHg and 1.1 mmHg, respectively [21]. These BP lowering effects have been observed in both hypertensive and normotensive individuals [36, 44]. Moreover, an inverse relationship between nitrate dosage and SBP reduction was observed [45]. The finding that only a higher dosage significantly reduced SBP suggests that a minimum amount of nitrate is needed to lower SBP [31]. For example, Hobbs *et al.* demonstrated that acute beetroot juice supplementation of 140, 350 and 700 mg provoked dose-dependent SBP reductions, with the latter two concentrations causing a significant decrease [36]. Likewise, Wylie *et al.* provided evidence that the similar type of supplementation caused a significant reduction in SBP when supplementing with 260 mg and a significant reduction in SBP and diastolic BP when supplementing with 520 mg of nitrate [46]. Moreover, Liu *et al.* investigated the acute effects of a meal rich in spinach containing 220 mg of nitrate and found a significant reduction in SBP [29]. Thus, these studies demonstrate that effects on the BP appear to occur after both nitrate supplementation and dietary nitrate consumption and that these decreases in BP are dose-dependent. Although most studies found only reductions in SBP and some did not even find a significant reduction in SBP and diastolic BP, there are plenty of studies that suggest that dietary nitrate has the potential to lower the BP [29, 30, 42, 47, 48]. However, currently there is a lack of studies investigating the long term effects (more than 4 weeks) of dietary nitrate on the BP, as only acute and short term effects on BP have been established [49, 50].

Once nitrate is in the body, it is converted to nitric oxide (NO) via the nitrate-nitrite-NO pathway (Figure 1). Nitrate from the diet concentrates in the salivary glands after which oral commensal bacteria reduce it to nitrite. Subsequently, nitrite in the saliva is further reduced to NO through enzyme activity [20, 26, 51]. NO mediates smooth muscle cell relaxation and vasodilation and because of these vasodilatory properties, dietary nitrate intake has the potential to reduce BP [52, 53].

Nitrate and cancer?

The assumption that eating too much nitrate in the form of vegetables would increase the risk of cancer has been around for a long time and some worry about eating too much nitrate-rich vegetables. This assumption arose as the combination between NO and proteins from the diet can result in the formation of nitrosamines, which are substances that are classified as 'probably carcinogenic to humans' by the International Agency for Research on Cancer [54-58]. Later on, the Dutch Organisation for Applied Scientific Research found that especially the combination of fish and nitrate-rich vegetables into one meal can cause extra

nitrosamines to be formed [56]. For this reason, the Netherlands Nutrition Centre recommended not to eat nitrate-rich vegetables in combination with fish [54]. In response, the Dutch National Institute for Public Health and the Environment researched this question and concluded that the acute and long term exposure to these nitrosamines pose a negligible risk on cancer in humans [59]. Subsequently, the recommendation not to eat too much nitrate and definitely not to combine it into one meal with fish were withdrawn. To conclude, the worries about the harmful effects of consuming too much nitrate are unfounded and, therefore, one should not be concerned about eating too much nitrate-rich vegetables.

Conclusion

In conclusion, for people with (pre)hypertension or with presence of cardiovascular risk factors, lifestyle interventions may be a plausible alternative to medication and even a conceivable way to prevent CVD progression. Especially the diet is an easy factor to influence and intervene in daily life. Since dietary nitrate has been observed to lower BP values in both normotensive and hypertensive individuals and due to the fact that acute and long term exposure to nitrosamines pose only a negligible risk on cancer, nitrate could be considered as a promising new lifestyle intervention targeting hypertension, thereby lowering the risk on several diseases, such as CVD. So, consuming a little bit extra beetroot or spinach would not hurt and could even benefit your BP!

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RECENT HIGH-IMPACT PAPERS FROM RADBOUDUMC RESEARCHERS

Simon Crox[1]

Summary

With over 3,000 publications per year, scientific research is a cornerstone of the Radboud university medical center [1]. In this section, recent high-impact papers with an impact factor higher than five – published by researchers from the Radboudumc – will be discussed.

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Revealing a tumor suppressor function in the liver using gene editing

Primary liver cancer is one of the most lethal cancers worldwide, displaying a very aggressive phenotype. However, the specific function of many genes involved in tumour formation is still mostly unknown. Breast cancer gene associated protein 1 (*BAP1*) is identified as a tumour suppressor gene and is investigated in order to understand tumour formation in cholangiocarcinoma, the most aggressive type of liver cancer [2]. This gene is highly relevant since it is mutated in 15 to 20% of the cases. Lisa van Voorthuijsen and Rik Lindeboom from the research theme of Cancer Development and Immune Defense, in collaboration with the Hubrecht Institute, used an innovative model to compare healthy and manipulated liver tissue, holding the mutated tumour suppressor gene *BAP1* [2]. Their results were published in Cell Stem Cell, a scientific journal (impact factor of 13). Organoids, mini organs that have been grown in a lab, were manipulated with gene editing techniques and were compared to their healthy control organoids [2]. The mutated organoids displayed characteristics of an invasive malignant tumour. Compared to their controls, they grew faster, turned into more solid masses, were more motile and tended to fuse together. Furthermore, the effect of *BAP1* was evaluated in organoids in which four genes were mutated that are known to form benign adenomas. When *BAP1* was manipulated in these adenomas, it had a catalytic effect on the transition into a malignant tumour. Importantly, the transition could be reversed by either adding normal cells or restoring the mutation of *BAP1* [2]. The researchers not only established important insights in *BAP1*, but displayed a relatively universal model that can be used to study many cancer genes in the future.

Rethink surgery in uncomplicated symptomatic gallstones

Gallstones symptoms are a major burden on Western society, as shown by a grand total of 1.8 million visits to the doctor annually in the United States of America alone [3]. Patients experience symptoms from passing stones, which is referred to as cholecystolithiasis. Five percent of these patients eventually develop complications such as cholecystitis, cholangitis or blockage of the pancreas causing a so-called biliary pancreatitis. Biliary colic, typical for cholecystolithiasis, is an episode of severe abdominal pain in the right upper quadrant lasting at least 15 to 30 minutes, according to the ROME III criteria (diagnostic criteria for symptomatic bile stones) [3]. However, most patients suspected of having bile stones do not experience this typical phenomenon but report non-specific symptoms. No consensus is available for cholecystectomy selection creating large variation between surgeons, hospitals and countries. But most importantly, persisting pain after cholecystectomy is high, ranging from 10 to 41% [3]. Kees van Laarhoven, professor of the Department of Surgery, and his colleagues investigated a stepwise restricted strategy with clear patient selection for cholecystectomy compared to standard care. A randomised multi-centre trial of 24 hospitals including 1,067 patients, was conducted in the Netherlands and published in The Lancet (impact factor of 43) [3]. Patients in the restricted strategy group only underwent cholecystectomy if they fulfilled five criteria based on the ROME III criteria. The trial showed that pain reduction was suboptimal in both groups after cholecystectomy. Although typical colics seemed to predict a better outcome of surgery on pain, the restrictive strategy did not show any advantages over standard care, suggesting limited validity of the ROME III criteria. In both groups, 37% of patients had persistent abdominal pain after surgery [3]. However, with a follow up of 12 months, the restricted group had significantly fewer cholecystectomies by almost eight percent. Moreover, there was no difference in gallstone complications, surgery complications or non-trial-related serious adverse events [3]. Physicians should, therefore, be encouraged to review their approach to presumed gallstone related abdominal symptoms. Consequently, this could decrease patient hospitalisation and lower the economic burden of cholecystectomies.

Robot interviews save healthcare professionals time

Patient-reported outcome measures (PROMs) are largely used in research and clinical work. Nowadays, assessment and filing of health status measures are a time-consuming task for every health care professional (HCP). Unfortunately, data collection using computers, smartphones or tablets can be especially difficult for the elderly. Moreover, completing forms on the internet has a non-response rate of 74%, which increases further with age [4]. There is a need for an alternative approach to free up time for HCPs, simultaneously acquiring robust PROMs. Social robots show good potential to aid in patient data collection. This friendly looking robot is over a meter tall, has voice recognition and face recognition to turn its head to the person talking [4]. Recently, Roel Boumans, Marcel Olde Rikkert and colleagues from the Department of Geriatrics tested their ability to independently conduct an interview in comparison to a human PROMs survey [4]. A nurse explained the purpose of the robot to an older volunteer. The robot presented the participants with dialogue options on a screen mounted to its chest. The majority of interviews were autonomously completed by the robot (93%) [4]. The time to complete the questionnaire did not differ from those performed by nurses. Importantly, agreement between the outcomes of frailty, resilience and well-being scores produced by the robot, compared to the nurses, was fair to good (41-80%). It should be noted that the robot's goal is not to replace a human job but to assist where necessary. Boumans *et al.* state that future research should look into implementation in clinical practice and integrate HCPs opinions to streamline the development of helper robots [4]. This study was published in the British Medical Journal Quality and Safety (impact factor of six).

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RAMS

A Word from the Board of RAMS

Dear reader,

Sadly, this is the end of the 14th edition of RAMS. What a ride it has been! All thanks to the wonderful people in our editorial board, reviewers and the (bio)medical students who provided us with their research. I would like to thank them all for their hard work.

We hope that closing the final page of this edition opens a door for you. It is the beginning of the academic year, you will be surprised by how much you can learn. We hope to inspire you to converting all that time and work spent studying, into something you are passionate about. Whether that is the influence of nutrition on our health, the health effects of social media or diagnosing skin cancer. Nothing motivates more than to learn with a clear goal in mind, such as getting published. Maybe we will be able to showcase what you have learned in one of the upcoming editions of RAMS.

The start of something new can be overwhelming and intimidating. Are we bringing the future a little too close? Maybe, but is there any harm in that? You might not be up to the task right now, but I am sure that this will change during the upcoming year. RAMS is changing as well. The attention is going to be shifted from workshops and lectures to the journal. A brand new board cannot wait to take the lead this year and work with our peers. We hope you will pick up our 15th edition!

On behalf of the board of RAMS,

Sasha Peerdeman
Treasurer of RAMS 2019-2020

General Board

RAMS is directed by the general board, which consists of five (bio)medical students. As members of the board they frequently meet to make sure all activities run smoothly. Moreover, they are in close contact with the supervisory board and the editorial staff. If you have any questions on general, promotional or financial subjects, please contact the general board of RAMS via voorzitter.rams@ru.nl.

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The editorial board, which consists of three (bio)medical students, is responsible for the contents of the journal, from reviewing the submitted papers to their rejection or publication. Furthermore, the editorial board is in charge of writing editorials and determining the general layout. For questions concerning the content of the journal please contact the editorial staff via hoofdredactie.rams@ru.nl. To submit papers, consult the 'for authors'-section on our website or mail to submit.rams@ru.nl.

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