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a clinical perspective**

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HABILITATIONSSCHRIFT

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from an epidemiological and a clinical perspective

Zur Erlangung der Venia Legendi der Universität Zürich

David Fäh

1. August 2009

Zusammenfassung der HABILITATIONSSCHRIFT

Modifiable risk factors of cardiovascular disease
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Zusammenfassung der Habilitationsschrift

Worldwide, cardiovascular diseases (CVD) are the leading cause of death. Several risk factors for CVD have been established, among which obesity, diabetes, hypertension, unfavourable lipid profile, physical inactivity and smoking are the most common. Most of these risk factors depend on diet, either by an excess of caloric intake and subsequent obesity or by a direct impact of nutrients. Recently, the role of sugar has received more attention. Its consumption has strongly increased in the past decades in the US but also in many European countries, including Switzerland. This increase was particularly strong for fructose and was mainly driven by mounting consumption of sugar sweetened drinks. Much more than glucose, fructose has an immediate impact on CVD risk factors. The consumption of large amounts of fructose can increase serum concentrations of cholesterol, glucose and uric acid, and may lead to higher blood pressure. However, the most pronounced change is an increase in serum triglycerides which may be accompanied by impaired insulin sensitivity.

While CVD rates generally go down in the western world, there has recently been a sharp increase in developing countries. These regions have skyrocketing population growth and thus deserve increasing attention. Representative for the future development of many developing countries is the recent history of the Republic of the Seychelles, located in the Indian Ocean. Since the construction of the airport in the 1970s, this country has experienced an accelerated epidemiological transition from a self-sustaining population living from agriculture and fishing to a service-orientated and consuming society. Along with an increasing buying power and the adoption of a western lifestyle, tobacco and heavy alcohol use have become more and more popular. Per capita caloric intake has increased substantially in the Seychelles and the consumption of sugar sweetened drinks has tripled in the past 25 years. In Switzerland, there has also been a rise in sugar intake, but the increase was less pronounced: per capita consumption increased from 41 to 48 kilo in the past 25 years. In 2001, each Swiss inhabitant consumed in average 105 litres of sugar sweetened drinks.

Surveys are an important tool to monitor diseases and risk factors in a population. Descriptive epidemiology can also be used to generate hypothesis about causal relationships which can thereafter be tested with clinical trials. Both approaches are necessary in order to detect and explore risk factors in a population. Based on these findings, public health measures aimed at reducing population risks can be developed and implemented.

The selected six publications highlight CVD risk factors from an epidemiological and clinical perspective. Three papers explore, on a population level, the development and the interaction of CVD risk factors and behaviours among each other and with disease parameters. The other three publications elucidate the direct impact of risk and protective factors on healthy humans. The first epidemiological study shows that the strong and fast increase in obesity prevalence in the Seychelles was not only paralleled by a rise of diabetes cases but also of persons with less severe impairments of glucose metabolism, such as impaired fasting glucose and impaired glucose tolerance [1]. A large

proportion of diabetes patients were not aware of the disease and about half of all diabetes cases was attributable to overweight and obesity. In-depth analysis showed that increasing BMI and deterioration of glucose metabolism were gradually associated with increasing insulin resistance. A second study revealed that not only diabetes but also less severe impairments of glucose metabolism go along with a deterioration of common CVD risk factors including hypertension, dyslipidemia and smoking [2]. Intima-media thickness of the carotid and femoral artery can be regarded as CVD outcome since it measures irreversible organic vascular changes, described as atherosclerosis. In this publication we also found that intima-media thickness gradually increased with increasing impairment of glucose metabolism. Interestingly, a part of these associations were still significant after adjustment for common CVD risk factors. This suggests that additional factors mediate the effect of glucose metabolism impairment on intima-media thickness. The analysis also revealed that adjustment for simple measurements (BMI and waist circumference) had similar impact as adjustment for common clinical CVD risk factors. This has practical relevance in that these simple measurements are valid tools for risk assessment in a population. A novel side-finding of this analysis was that the relationships between impaired glucose metabolism and intima-media thickness tended to be larger at femoral than carotid levels independently of adjustment. Accordingly, one can speculate whether measurement at femoral site could be more useful for risk assessment.

The two studies show that CVD risk factors can rapidly increase in developing countries and may reach or exceeded levels typically found in middle- or high-income countries. This increase is mainly driven by fundamental changes in lifestyle. Simple and inexpensive risk monitoring – for example the assessment of BMI, family history of CVD and diabetes and capillary glucose level - can be as effective as much more extensive examinations. In view of the strong association, early prevention of factors leading to obesity is a cornerstone strategy to curb CVD and their risk factors.

Disadvantageous risk behaviours usually do not occur isolated. They mostly coincide with others and build clusters. This is also the case for smoking, cannabis use and heavy alcohol consumption. Youth who start with one of these behaviours frequently continue with another. This finding of the third epidemiological publication has several public health implications [3]. It is important to adopt healthy behaviours early in life since this has the potential to reduce CVD in adulthood. Furthermore, clustering of risk factors emphasizes the need to address these behaviours within a comprehensive and integrated approach.

As suggested by the epidemiological studies, sugar sweetened drinks may play an important role as CVD risk factor. This was substantiated by the first clinical study that found a strong increase in serum triglycerides following high fructose intake during a short period [4]. This increase was driven by a boosted hepatic de novo lipogenesis and accompanied by insulin resistance a potential precursor of diabetes. As a possible CVD protective factor, fish oil was thought to prevent metabolic alterations induced by fructose. This was however only the case for a part of the increase in serum triglycerides. Because the high amounts of administered fructose and the short duration of feeding

represented a somewhat unrealistic condition, a second protocol has been developed. Fructose administration was prolonged to four weeks but the amount was halved and now corresponded to the realistic daily consumption of about 1.5 litres of soda [5]. In view of the strong increase of de novo lipogenesis, hepatic fat accumulation could be expected. Therefore, magnetic resonance spectroscopy was used in the second study to measure changes in intrahepatic fat. In healthy young men, the lower fructose dose led to increased triglyceride and glucose levels but neither to insulin resistance nor to intrahepatic fat accumulation. However, alterations in the later two were found in one healthy subject who had a first degree relative with type 2 diabetes. This subject had to be excluded from the study but constituted a basis for a consecutive study which is not discussed here.

In the second clinical study, muscle and adipose tissue biopsies were taken from each subject. With these samples, changes in expression of 16 genes involved in lipid, sugar and energy metabolism were measured. The results were published in a third paper [6]. The expression of a lipogenic enzyme was increased. This enzyme favours lipid deposition in muscles and is associated with liver steatosis and insulin resistance. In contrast, the expression of an insulin-stimulated receptor was decreased after fructose intake, which could be interpreted as first step towards insulin resistance. An activator protein that stimulates mitochondrial biogenesis also tended to be less expressed after fructose consumption. These findings suggest that an increase in fat deposition in hepatic and muscle cells could indeed be expected from fructose consumption. However, the duration of administration was probably too short for these young healthy and normal weight males without family history of diabetes.

In conclusion, the fast increase in CVD in many parts of the world is mainly due to modifiable risk factors. Particularly for rapidly developing countries, the emerging CVD epidemic is a major burden because these countries do not have sufficient resources to effectively monitor, prevent and treat CVD. Epidemiological research suggests that the consumption of sugar sweetened drinks could be a factor contributing to this increase in CVD. These drinks contain large amounts of fructose, a type of sugar whose consumption has over proportionally increased in the past years. Clinical research has shown that even amounts typically consumed can lead to metabolic deteriorations which increase CVD risk. However, the harmfulness of the effect of fructose strongly depends on the amount ingested. Dose dependence applies for most risk factors as well as the fact, that they rarely occur alone and that their impact varies significantly between individuals. Fructose is a risk factor that could particularly easily be modified because the main source are sugar sweetened drinks. A ban of distributors in schools, a stricter regulation of advertisement and a tax on sugar sweetened drinks could effectively and inexpensively reduce fructose intake. To assess changes in risk factors in a population, few simple measurements are almost as effective as extensive assessments. Inexpensive monitoring and prevention of risk factors are of major importance in resource-constrained settings as found in developing countries. From a public health perspective both epidemiological and clinical approaches are necessary to elucidate the impact of CVD risk factors and the potential for prevention.

Publications selected for habilitation

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