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TRIIN EGLIT

Obesity, impaired glucose regulation, metabolic syndrome and their associations with high-molecular-weight adiponectin levels

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Department of Internal Medicine, University of Tartu, Estonia

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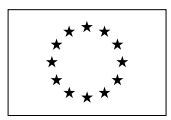

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1. LIST OF ORIGINAL PUBLICATIONS

Paper I: Eglit T, Ringmets I, Lember M. Obesity, high-molecular-weight (HMW) adiponectin, and metabolic risk factors: prevalence and gender-specific associations in Estonia. PLoS One 2013;8:e73273.

Paper II: Eglit T, Rajasalu T, Lember M. Prevalence of diabetes and impaired glucose regulation in Estonia. Diabet Med 2011; 28:504–5.

Paper III: Eglit T, Rajasalu T, Lember M. Metabolic syndrome in Estonia: prevalence and associations with insulin resistance. Int J Endocrinol 2012;2012:951672.

Paper IV: Eglit T, Lember M, Ringmets I, Rajasalu T. Gender differences in serum high-molecular-weight adiponectin levels in metabolic syndrome. Eur J Endocrinol 2013;168:385–91.

Contribution of Triin Eglit to the preparation of the original publications: study design, examination of patients, data collection, statistical data analysis, and writing of the manuscript of all 4 original publications.

2. ABBREVIATIONS

ADA	American Diabetes Association
AdipoR	Adiponectin receptor
AHA/NHLBI	American Heart Association/National Heart, Lung, and Blood Institute
AMPK	Adenosine monophosphate-activated protein kinase
AUROC	Area under the receiver operating characteristic curve
BMI	Body mass index
CRP	C-reactive protein
CT	Computer tomography
DECODE	Diabetes Epidemiology Collaborative analysis of Diagnostic criteria in Europe
FFA	Free fatty acids
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HMW	High-molecular-weight
HOMA	Homeostasis model assessment
HOMA-IR	Homeostasis model assessment of insulin resistance
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL	Interleukin
IR	Insulin resistance
LDL	Low density lipoprotein
LMW	Low-molecular-weight
MRI	Magnet resonance imaging
MS	Metabolic syndrome
NAFLD	Nonalcoholic fatty liver disease
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NHANES	National Health and Nutrition Examination Survey
OECD	Organisation for Economic Cooperation and Development
OGTT	Oral glucose tolerance test
PAI-1	Plasminogen activator inhibitor-1
PCOS	Polycystic ovary syndrome
TNFα	Tumor necrosis factor alpha
WHO	World Health Organization

3. INTRODUCTION

The worldwide prevalence of obesity has nearly doubled between 1980 and 2008 (Finucane et al 2011). Globally, 35% of adults aged ≥20 years were overweight (BMI ≥25 kg/m^2) and 11% were obese (BMI ≥30 kg/m^2) in 2008. Overweight and obesity are linked to more deaths worldwide than underweight (World Health Organization 2013). The rapid increase in worldwide rates of overweight and obesity over the last 30–40 years suggests a predominant change in environmental, diet, and lifestyle factors rather than any change in genetics as the main cause of the obesity epidemic. On the other hand, the observation that the loss of the function of certain genes in human leads to either severe obesity, early diabetes, or severe insulin resistance challenges the view that environmentally driven obesity leads to insulin resistance which leads to type 2 diabetes (Murphy et al 2013). However, there is a wide spectrum ranging from genetically determined obesity to behaviourally determined obesity, while in most individuals these factors are mixed (gene-environment interaction) (Clement et al 2010). Obesity is associated with hypertension, diabetes, hyperlipidaemia, coronary heart disease, liver disease, heart failure, respiratory failure, asthma, cholelithiasis, osteoarticular diseases, and cancers as well as with psychological disorders such as depression, which reduce the quality and length of life (Clement et al 2010). Many of the comorbidities of obesity are reflected in metabolic syndrome (Haslam et al 2005). The metabolic syndrome is a clustering of risk factors (glucose intolerance, obesity, elevated blood pressure and dyslipidaemia) which predispose an individual to cardiovascular morbidity and mortality (Day 2007). Obesity is the most important modifiable risk factor before metabolic syndrome develops and central obesity precedes deterioration in each of the components that consitute the metabolic syndrome (Cameron et al 2009). However, a subset of obese subjects seems to be protected from obesity-related cardiovascular and cardiometabolic abnormalities and this obesity phenotype is described as metabolically normal obesity or metabolically healthy obesity (Pataky et al 2010).

Insulin resistance is implicated in the pathophysiology of the twin epidemic of type 2 diabetes and obesity (Murphy et al 2013). There is no universally accepted key mechanism underlying metabolic syndrome, although insulin resistance and central obesity have both been proposed for this role (Simmons et al 2010).

Adipose tissue modulates metabolism by releasing non-esterified fatty acids and glycerol, and hormones including leptin and adiponectin, as well as proinflammatory cytokines (Kahn et al 2006). Adiponectin has insulin-sensitizing, anti-inflammatory, anti-atherogenic and cardioprotective properties and, unlike most other adipokines, circulating levels of adiponectin are reduced in obesity and associated diseases (Scherer 2006). Adiponectin is secreted into the circulation as low-molecular-weight (trimers and hexamers) and high-molecular-weight (HMW) multimers with the latter being more metabolically active (Simpson et al 2010). There is a clear gender difference in HMW adiponectin

levels: women have significantly higher HMW adiponectin concentration compared with men, whereas there were no gender differences for the other two forms (Xu et al 2005). Certain obese individuals have adiponectin levels similar to those found in subjects with normal body mass index (BMI), which is associated with the metabolically healthy obese phenotype (Aguilar-Salinas et al 2008). Data about HMW adiponectin levels in metabolically healthy obese subjects is scarce (Bik et al 2010, Elisha et al 2010).

4. REVIEW OF THE LITERATURE

4.1. Definitions of overweight and obesity, imapired glucose regulation and metabolic syndrome

4.1.1. Definitions of overweight and obesity

According to the World Health Organization (WHO), obesity is defined as a condition of abnormal or excessive fat accumulation in the adipose tissue, to the extent that health may be impaired (World Health Organization 2000). Of the five anthropometric indices for diagnosing obesity – BMI, body fat percentage, waist circumference, waist-to-hip ratio and waist-to-stature ratio – the most commonly used index around the world is BMI (Cheng 2004). BMI is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person`s weight in kilograms divided by the square of his\her height in meters (kg/m^2). The classification of overweight and obesity according to BMI is shown in Table 1 (World Health Organization 2000). Obesity is defined as a BMI ≥ 30.0 (World Health Organization 2000).

Table 1. WHO classification of adults according to BMI

Classification	BMI	Risk of comorbidities
Underweight	<18.5	Low (but increased risk of other clinical problems)
Normal range	18.5–24.9	Average
Overweight	≥25.0	
Preobese	25.0–29.9	Increased
Obese class I	30.0–34.9	Moderate
Obese class II	35.0–39.9	Severe
Obese class III	≥40.0	Very severe

Although BMI is a convenient tool to define obesity it does not take into account body composition (fat mass and fat-free mass distribution) (World Health Organization 2000, Clement et al 2010, Gomez-Ambrosi et al 2012). A recent cross-sectional study from Spain showed that 29% of subjects classified as lean and 80% of individuals classified as overweight (pre-obese) according to BMI had body fat percentage (estimated by air displacement plethysmography) within the obesity range (≥25.0% for men and ≥35.0% for women). Thus BMI, although being an extremely valuable tool for epidemiological studies, may underestimate body fat percentage, especially in the overweight category, and the actual cut-off points that can more accurately diagnose obesity may be different: 29 kg/m^2 for men and 27 kg/m^2 for women (Gomez-Ambrosi et al 2012). Evidence suggests that intra-abdominal visceral fat accumulation rather than BMI is related to the dysfunction of adipocytes and cardiometabolic disorders in obesity (Kishida et al

2011). Furthermore, findings from large prospective cohort studies show that the association of risk of cardiovascular disease and death with increasing waist circumference is stronger in non-obese compared with obese individuals (Stefan et al 2013). In 2008, WHO Expert Consultation published a report "Waist Circumference and Waist-Hip Ratio" which found that an increase of the waist circumference and the waist-hip ratio is associated with increased disease risk. These measures of abdominal obesity were correlated with BMI, but the level of associations varied, suggesting that these measures may provide different information and thus may not be interchangeable. However, further studies are needed to establish whether the recommended waist circumference cut-off points should be specific to sex, age and population (World Health Organization 2008). In patients with abdominal obesity, adipocytes are accumulated into two compartments: subcutaneous fat and visceral fat, the latter considered as being more pathogenic (He et al 2010). Although BMI may be below 25 kg/m^2, visceral fat may be increased; thus measuring waist circumference becomes particularly important in people with lower BMI (Cheng 2004). Furthermore, waist circumference does not precisely represent the entire abdominal fat compartments. Visceral fat obesity (defined as a visceral fat area of $\geq$100 cm^2 measured by computer tomography (CT)) can occur in subjects with normal body weight and normal waist circumference. Therefore, exact assessment of abdominal adipose tissue requires more comprehensive technology, such as CT, magnet resonance imaging (MRI), and ultrasound (He et al 2010).

4.1.2. Comparison of WHO and American Diabetes Association (ADA) definitions for impaired glucose regulation

Definitions for impaired glucose regulation have been developed and agreed with both by WHO and ADA. Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Diabetes classification involves four main types of diabetes: type 1, type 2, other specific types and gestational diabetes. Type 2 diabetes, which accounts for ~90–95% of those with diabetes, encompasses individuals who have insulin resistance and usually relative insulin deficiency. Type 1 diabetes accounts for only 5–10% of those with diabetes and results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas (American Diabetes Association Position Statement 2013). The long-term relatively specific effects of diabetes include development of retinopathy, nephropathy and neuropathy. People with diabetes are also at increased risk of cardiac, peripheral arterial and cerebrovascular disease (World Health Organization 2011). Diabetes and impaired glucose tolerance (IGT) are defined similarly by WHO and ADA. Both ADA and WHO agree that glycated haemoglobin (HbA1c) of 6.5% (48 mmol/mol) is recommended as the cut-off point for diagnosing diabetes and a value less than 6.5% (48 mmol/mol) does not exclude diabetes diagnosed by using glucose tests (World Health Organization 2011, International Expert Committee 2009) (Table 2). In contrast, the fasting plasma

glucose cut-off point for impaired fasting glucose (IFG) is 6.1 mmol/l according to the WHO criteria (World Health Organization 2006), but 5.6 mmol/l according to the ADA criteria (Genuth et al 2003) (Table 2). In Estonia, impaired glucose regulation is diagnosed according to the WHO criteria (Eesti Endokrinoloogia Selts, Eesti Perearstide Selts 2008) and a national guideline for using HbA1c to diagnose diabetes was published in 2012 (Rajasalu 2012).

IFG and IGT represent metabolic states intermediate between normal glucose homeostasis and diabetic hyperglycaemia (Unwin et al 2002). The ADA classifies IFG, IGT and also HbA1c value in the range of 5.7–6.4% (39–46 mmol/mol) as prediabetic conditions (American Diabetes Association Position Statement 2013). In contrast, WHO considers that there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below 6.5% (48 mmol/mol) (World Health Organization 2011). The Estonian national guideline does not define prediabetes by HbA1c, but still recommends to perform an oral glucose tolerance test (OGTT) for subjects having HbA1c 6.0–6.4% (42–46 mmol/mol) (Rajasalu 2012). A recent meta-analysis showed that IFG and IGT are associated with modest increase in the risk for cardiovascular disease (Ford et al 2010). Prediabetes often progresses to overt diabetes within a few years and may be associated with increased risk of microvascular and macrovascular complications (Moutzouri et al 2011).

Table 2. Comparison of the WHO and ADA definitions of impaired glucose regulation

	WHO 2011	**ADA 2013**
Diabetes		
Fasting plasma glucose	≥7.0 mmol/l	≥7.0 mmol/l
	or	or
2-hour plasma glucose in OGTT	≥ 11.1 mmol/l	≥ 11.1 mmol/l
	or	or
Random glucose*		≥ 11.1 mmol/l
		or
HbA1c	≥6.5% (≥48 mmol/mol)	≥6.5% (≥48 mmol/mol)
Impaired glucose tolerance (IGT)		
Fasting plasma glucose	<7.0 mmol/l	
	and	
2-hour plasma glucose in OGTT	7.8–11.0 mmol/l	7.8–11.0 mmol/l
Impaired fasting glucose (IFG)		
Fasting plasma glucose	6.1–6.9 mmol/l	5.6–6.9 mmol/l
	and	
2-hour plasma glucose in OGTT	<7.8 mmol/l	
Prediabetes		
Fasting plasma glucose		5.6–6.9 mmol/l
		or
2-hour plasma glucose in OGTT		7.8–11.0 mmol/l
		or
HbA1c		5.7–6.4% (39–46 mmol/mol)

* in patients with classic symptoms of hyperglycaemia

4.1.3. Review of the definitions of metabolic syndrome

Metabolic syndrome (MS) is a complex of interrelated risk factors for cardiovascular disease and diabetes (Alberti et al 2009). In 1988, Reaven defined syndrome X, a cluster of risk factors for coronary artery disease, which involved resistance to insulin stimulated glucose uptake, glucose intolerance, hyperinsulinaemia, increased level of triglycerides, decreased level of high-density lipoprotein (HDL) cholesterol and hypertension (Reaven, 1988). Thereafter, various diagnostic criteria of MS have been proposed by different organizations. The first formal definition of the metabolic syndrome was published by the WHO in 1998 and this focused primarily on the presence of insulin resistance which was defined by hyperinsulinaemia, IGT or type 2 diabetes. In addition, two of the following criteria, dyslipidaemia, hypertension and microalbuminuria, also had to be present (Alberti et al 1998). Shortly thereafter (in 1999), an alternative definition of metabolic syndrome was proposed by the European Group for the Study of Insulin Resistance (EGIR). The metabolic syndrome was defined by the presence of insulin resistance or fasting hyperinsulinaemia plus two of the following criteria: fasting plasma glucose ≥6.1 (but non-diabetic), hypertension, dyslipidaemia and central obesity (Balkau et al 1999). In 2001, a new definition of metabolic syndrome was published by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), which defined metabolic syndrome as the presence of three or more of the following: abdominal adiposity, dyslipidaemia, elevated fasting glucose and elevated blood pressure (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The NCEP ATP III definition differed from both the WHO and the EGIR definitions in that insulin resistance was not considered as a necessary diagnostic component (Kassi et al 2011). Most recent definitions include the NCEP ATP III criteria developed by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) (Grundy et al 2005) and the International Diabetes Federation (IDF) criteria (Alberti et al 2005). The IDF criteria involved population-specific waist circumference plus any two of the following: dyslipidemia, hypertension, fasting glucose ≥5.6 mmol/l (Alberti et al 2005). The remaining four components of metabolic syndrome in the AHA/NHLBI definition were identical to those of the IDF, although abdominal obesity was defined differently. The IDF recommended that the threshold for waist circumference in Europeans should be 94 cm for men and 80 cm for women, while the AHA/NHLBI recommended cut-off points of 102 and 88 cm, respectively (Kassi et al 2011). In 2009, a Joint Interim Statement, which represented the outcome of an attempt to unify the criteria of metabolic syndrome by several major organizations, was published (Alberti et al 2009). According to this statement, presence of any three of the following five risk factors shown in Table 3 constitutes a diagnosis of MS (Alberti et al 2009).

Table 3. Joint Interim Statement criteria for the clinical diagnosis of metabolic syndrome

Measure	Categorical cut points
Elevated waist circumference	Population- and country-specific definitions[1] AHA/NHLBI (ATP III) cut-off points: ≥102 cm for males ≥88 cm for females
Elevated triglycerides or drug treatment for elevated triglucerides	≥1.7 mmol/l
Reduced HDL cholesterol or drug treatment for reduced HDL cholesterol	<1.0 mmol/l for males <1.3 mmol/l for females
Elevated blood pressure or antihypertensive drug treatment in a patient with a history of hypertension	Systolic ≥ 130 and /or diastolic ≥ 85 mm Hg
Elevated fasting glucose or drug treatment of elevated glucose	≥5.6 mmol/l

[1] It is recommended that the International Diabetes Federation (IDF) cut-off points should be used for non-Europeans and either the IDF or AHA/NHLBI cut-off points should be used for people of European origin until more data are available.

4.2. Epidemiology of overweight and obesity, impaired glucose regulation and metabolic syndrome

4.2.1. Prevalence of overweight and obesity

The prevalence of overweight and obesity is increasing at an alarming rate in developed and developing countries throughout the world. Before 1980, obesity rates were generally below 10% worldwide, but since then, rates have doubled or tripled in many countries, an in almost half of the Organization for Economic Cooperation and Development (OECD) countries 50% or more of the population is overweight (Sassi 2010). The health risks associated with obesity and overweight make it a particularly relevant public health challenge worldwide. Overall, 23.2% of the world's adult population in 2005 were overweight (24.0% of men and 22.4% of women) and 9.8% were obese (7.7% of men and 11.9% of women) (Kelly et al 2008). In 2008, an estimated 1.46 billion adults worldwide had BMI of 25 kg/m^2 or greater, of these 205 million men and 297 million women were obese. Worldwide, the age-standardised prevalence of obesity was 9.8% for men and 13.8% for women in 2008, which was nearly twice the prevalence of 4.8% for men and 7.9% for women in 1980 (Finucane et al 2011). If the current trends continue, over 50% of adults in the United States will be obese by 2030. (Walley et al 2009). On the other hand, data from the National Health and Nutrition Examination Survey (NHANES) showed that 34.9% of adults in United States were obese in 2011–2012, while the overall prevalence

did not differ between men and women and the prevalence of obesity among adults did not change between 2009–2010 and 2011–2012 (Ogden et al 2013). The prevalence of obesity in Europe ranges between 10–25% for men and 10–30% for women (Tsigos et al 2008). Rates of overweight and obesity have been increasing over the past three decades everywhere in the OECD countries and projections suggest that if recent trends continue over the next ten years, the pre-obesity (BMI 25–29.9 kg/m^2) rates for the 15–74 age group will stabilise and may even shrink slightly in many countries, while obesity rates continue to rise (Sassi 2010). To date, the prevalence of obesity in Estonia has only been estimated from self-reported data from posted questionnaire surveys. In 2008, among subjects aged 16–64, it was just 17.5% for men and 18.0% for women (Tekkel et al 2009). According to the WHO data, the prevalence of overweight (BMI≥25) and obesity (BMI≥30) among Estonians aged ≥20 years in 2008 was estimated to be 53.7% and 20.6%, respectively (World Health Organization 2011b). No population-based study using objective measurements of weight and height has been conducted in Estonia.

4.2.2. Prevalence of impaired glucose regulation

4.2.2.1. Prevalence of diabetes

The prevalence of diabetes and impaired glucose regulation is rapidly increasing worldwide (Shaw et al 2010). Type 2 diabetes accounts for 90–95% and type 1 diabetes accounts for only 5–10% of adults with diabetes (American Diabetes Association Position Statement 2013). Type 1 diabetes is the most common metabolic disease in childhood and the European region displays the highest prevalence of type 1 diabetes in children (International Diabetes Federation 2013). In Estonian children aged 0–14.9 years, the age-standardized incidence rate of type 1 diabetes for the period between 1999 and 2006 was 17.2 (Teeäär et al 2010). According to the global report of 2010, the worldwide prevalence of diabetes among 20–79-year-old adults was estimated to be 6.4% (285 million), which is projected to rise 7.7% (439 million) by 2030. The estimates for both 2010 and 2030 showed a slight gender difference in the number of people with diabetes (Shaw et al 2010). The prevalence of diabetes increases with age: pooled data from 13 European cohorts showed that the prevalence of diabetes was <10% in subjects younger than 60 years and between 10–20% at the age of 60–79 years (DECODE Study Group 2003). According to the most recent global report (International Diabetes Federation 2013), the worldwide prevalence of diabetes among 20–79-year-old adults was estimated to be 8.3% (382 million) in 2013, which is projected to rise to 10.1% (592 million) by 2035. Almost half of all adults with diabetes are between the ages of 40 and 59 years. The number of people with diabetes in Europe in 2013 was estimated to be 56.3 million, or 8.5% of the adult population. The country with the highest prevalence (14.9%) is Turkey, followed by Montenegro, Macedonia, Serbia, and Bosnia and Herzegovina (International Diabetes Federation 2013). The latest

projections of diabetes prevalence are considerably higher than earlier predictions: in 2000 the worldwide prevalence of diabetes for all adults ≥20 years of age was estimated to be 2.8% (171 million), which was projected to rise 4.4% (366 million) by 2030 (Wild et al 2004). The accuracy of global estimates is hampered by the shortage of data on the prevalence of diabetes in particular regions, including Eastern Europe (Wild et al 2004, Shaw et al 2010). For Estonia, so far, data has been extrapolated from Polish data of different sources (personal communication and (Szurkowska et al 2001) and the estimated prevalence was 4.4% for 2000 (Wild et al 2004) and 9.9% for 2010 (Shaw et al 2010). The marked increase in this indicator is most probably attributable to different data sets used for extrapolation. A smaller study conducted in 2006 in one region of Estonia indicated that the prevalence of diabetes among Estonian adults might be as high as 8.7% (Rajasalu et al 2008). However, in the latest IDF Diabetes Atlas our population-based study (Eglit et al 2011) was used as one of the data sources and the national prevalence of diabetes in Estonia was estimated to be 7.7% (Intenational Diabetes Federation 2013).

4.2.2.2. Prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)

In the majority of populations studied, IGT is more prevalent than IFG, and there is a difference in the phenotype and gender distribution between these two categories. The IFG is significantly more common among men and IGT is slightly more common among women. The prevalence of IFG tends to plateau in middle age whereas the prevalence of IGT rises up old age (Unwin et al 2002). According to the results of the NHANES conducted in 2005–2006 and including 1547 nondiabetic adults, the prevalence of both IFG and IGT was 9.8% and the prevalence of IGT alone was 5.4% (Karve et al 2010). According to the most recent global report, in 2013 approximately 316 million (6.9%) in the age group 20–79 years had IGT, which can be projected to increase to 471 million (8.0%) among the adult population by 2035 (International Diabetes Federation 2013). The majority of adults with IGT are under the age of 50, and if left untreated, are at a high risk of progressing to type 2 diabetes in later life (International Diabetes Federation 2013).

4.2.3. Prevalence of metabolic syndrome

The prevalence of MS is increasing globally, without any universal or gender-specific differences (Cornier et al 2008). Comparison of prevalence data for different populations is difficult because many studies compare prevalence rates by using different criteria of the metabolic syndrome (Eckel et al 2005). However, no matter which criteria are used, the prevalence of metabolic syndrome is high and rising in all Western societies, probably as a result of the obesity epidemic (Kassi et al 2011). Among adults in the United States, the prevalence

of ATP III-defined MS increased from 23.7% in 1988–1992 to 34.6% in 1999–2002 (Ford et al 2002, Ford 2005). While the prevalence of MS is lower in Northern and Mediterranean Europe, it is increasing in many less developed nations (Batsis et al 2007). The Diabetes Epidemiology Collaborative analysis of the Diagnostic criteria in Europe (DECODE) Study, including pooled data from nine European population-based cohorts, showed that the prevalence of metabolic syndrome was 32.2% and 28.5% for men and women, respectively (Qiao 2006). A very consistent finding across different ethnic groups indicates that the prevalence of metabolic syndrome is highly age-dependent (Eckel et al 2005). The prevalence of the metabolic syndrome increases even more dramatically (compared with the increase with age) with increasing BMI. However, it should be noted that even lean individuals may develop metabolic syndrome, which demonstrates the complexity of its pathogenesis (Kassi et al 2011).

The Estonian population has undergone a rapid transition towards a Western sedentary lifestyle over the last decades and the prevalence of metabolic syndrome has not been previously studied in Estonia.

4.3. Adipose tissue distribution and functions

Adipose tissue is a complex and highly active metabolic and endocrine organ and the traditional concept of adipose tissue as a passive reservoir for energy storage is no longer valid (Kershaw et al 2004). There are two types of adipose tissue depending on its cell structure, location, colour, vascularization and function: white adipose tissue and brown adipose tissue (Vazgues-Vela et al 2008). Brown fat was once thought to have a functional role only in rodents and human infants; however, recent studies using ^{18}F-labelled 2-deoxy-glucose positron emission tomography (PET) in combination with CT clearly demonstrated the presence of metabolically active brown fat in adult humans (Schulz et al 2013). The most common location of brown fat is the neck and the supraclavicular area (Paidisetty et al 2009). Brown adipose tissue uses energy to produce heat through non-shivering thermogenesis. Obese individuals have 25% decreased activation of this tissue after cold exposure and women appear to have more active brown adipose tissue than men (Clement et al 2010). Like white adipose tissue, brown adipose tissue can affect whole-body metabolism and its activation might lead to new approaches to promoting weight loss and increasing insulin sensitivity (Hassan et al 2012).

The functions of white adipose tissue can be classified in three aspects: first, it is related to lipid metabolism including triglycerides storage and fatty acids release; second, it catabolizes triglycerides in order to release glycerol and fatty acids that participate in glucose metabolism in the liver and other tissues and, third, it secretes adipokines (Vazgues-Vela et al 2008). Additionally, white adipose tissue can act as a thermal insulator and protect other organs from mechanical damage (Hassan et al 2012). In humans, adipose tissue is located beneath the skin (subcutaneous adipose tissue), around internal organs (visceral adipose

tissue), in bone marrow (yellow bone marrow), and in breast tissue (Hassan et al 2012). Fat mass is dependent on both adipocyte cell number and size. The number of adipocytes is determined during early adulthood and changes in fat mass are attributed to changes in adipocyte cell size. Large adipocytes are more insulin-resistant and lipolytic, and release more inflammatory cytokines and less adiponectin (Gustafson 2010). Gender differences in deposition of body fat are evident even at the foetal stage. After adjusting for differences in height, men have higher total lean mass and bone mineral mass, and lower fat mass compared with women. Also men have relatively higher central distribution of fat while women have a more peripheral distribution of fat (World Health Organization 2008). Visceral fat accounts for ~20% of total body fat in men compared with only ~6% in pre-menopausal women (Gustafson 2010). However, pregnancy and menopause are associated with an increase in fat mass in women, and a redistribution of fat to the abdominal area (World Health Organization 2008). It has been speculated that the reduced tendency to accumulate fat within intraabdominal sites may be one of the primary metabolic differences underlying the reduced risk of cardiovascular disease, metabolic syndrome, and diabetes in women (Regitz-Zagrosek et al 2006).

4.4. White adipose tissue as an endocrine organ

White adipose tissue is an active endocrine organ that releases a large number of bioactive mediators (adipokines) modulating haemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis (Rabe et al 2008). White adipose tissue contains different cell types: one third of the tissue consists of adipocytes and the rest consists of fibroblasts, macrophages, stromal cells, monocytes and preadipocytes (Vazgues-Vela et al 2008). Mature adipocytes are the main source of leptin and adiponectin; macrophages produce almost all tumour necrosis factor alpha (TNFα), resistin and visfatin, while prostaglandin E2, interleukins, vascular endothelial growth factor and hepatocyte growth factor are synthesized by stromal and vascular cells (Gnacinska et al 2009). Visceral adipose tissue secretes higher levels of complement factors, adiponectin, and inflammatory markers such as interleukin 6 (IL6), IL8, angiotensinogen and plasminogen activator inhibitor-1 (PAI-1), while abdominal subcutaneous fat is probably the main source of increased levels of circulating free fatty acids (FFA) (Gustafson 2010). So far as many as 100 substances synthesized by white adipose tissue have been discovered (Gnacinska et al 2009). Among these, adiponectin and leptin are the most abundant adipocytokines produced by adipocytes (Tilg et al 2006) and adiponectin has gained considerable attention because of its antidiabetic, antiatherogenic and anti-inflammatory properties; furthermore, it has an important protective role in carcinogenesis (Brochu-Gaudreau et al 2010).

4.5. Obesity and metabolic syndrome: pathogenesis (focused on adipose tissue dysfunction) and clinical significance

4.5.1. Obesity

4.5.1.1. Factors associated with development of obesity

The accumulation of body fat in obese people indicates the failure of the body`s systems to ensure proper energy homeostasis by adjusting for environmental influences, behaviour, psychological factors, genetic make-up and neurohormonal status (Clement et al 2010). The Big Two explanations proffered for the obesity epidemic are reduced physical activity and specific food manufacturing and marketing practices (Keith et al 2006). It is clear that through "over-nutrition", glucose, lipids and endotoxin can affect different tissues to mediate an aberrant inflammatory response and advance the pathogenesis of insulin resistance and metabolic disease; therefore, dysfunctional diets might provide the key targets for intervention (Piya et al 2013). However, there are several other additional putative contributors which might explain the increase of obesity: sleep deprivation, endocrine disruptors, reduction in variability in ambient temperature, decreased smoking, pharmaceutical iatrogenesis, changes in distribution of ethnicity and age, increasing gravid age, intrauteral and intergenerational effects. Higher BMI is associated with better reproductive fitness-yielding selection for obesity-predisposing genotypes and assortative mating (Keith et al 2006). In addition, studies have suggested that disruption of the circadian system or chronodisruption (shift work, sleep deprivation and exposure to bright light at night) may also lead to obesity (Garaulet et al 2010). A novel factor identified to have a role in human obesity and associated metabolic risks is the commensal microbiota of the intestine or the gut microbiota (Clement 2011). There is also growing evidence about the link between obesity and low circulating 25-hydroxyvitamin D concentrations, but the cause-effect relationship remains unclear in this case (Earthman et al 2012). According to the thrifty genotype hypothesis, the high prevalence of type 2 diabetes and obesity is a consequence of genetic variants that have undergone positive selection during historical periods of erratic food supply. However, no consistent pattern of selection that could provide conclusive confirmation of the thrifty genotype hypothesis was found by Southam *et al* who analysed 17 loci of type 2 diabetes and 13 loci of obesity (Southam et al 2009). In conclusion, it is clear that the worldwide epidemic of obesity is not of genetic origin but is due to changes in the lifestyle and environment. However, it is also clear that genetic factors greatly influence who gains weight as well as the magnitude of weight gain, placing individuals in the same "obesogenic" environment at significantly different risks of becoming obese (Haslam et al 2005, Walley et al 2009, Dixon 2010).

4.5.1.2. Adipose tissue dysfunction in obesity

Obesity is characterized by increased storage of fatty acids in an expanded adipose tissue mass and altered adipokine production, which is closely associated with the development of insulin resistance in peripheral tissues such as skeletal muscle and the liver (Figure 1) (Galic et al 2010). Excessive adipose tissue can contribute to inflammation in two ways: ectopic fat storage induces lipotoxicity, promoting an intracellular inflammatory response, and altered adipokine production in obesity contributes to the inflammatory response. Adiponectin has a role in both of these processes (Whitehead et al 2006). It is well established that where there is an expansion of adipose tissue, such as that observed in obesity, there is a sustained inflammatory response accompanied by adipokine dysregulation, which leads to chronic subclinical inflammation as well as insulin resistance. While adipose tissue from lean individuals may preferentially secrete anti-inflammatory adipokines such as adiponectin, transforming growth factor β (TGFβ), IL10, IL4, IL13 and apelin, then in obesity there are released pro-inflammatory adipocytokines such as TNFα, IL6, leptin, visfatin, resistin, angiotensin II and PAI-1, as well as several interleukins coupled with a reduction in secretion of anti-inflammatory adipokines (Piya et al 2013).

Adipokines, such as adiponectin, leptin, resistin and visfatin, provide an important link between obesity, insulin resistance, and related inflammatory disorders (Tilg et al 2006). The functionality of white adipose tissue cells involves the integration of several biochemical pathways: lipogenesis, lipolysis and fatty acids oxidation. Maintenance of equilibrium of these pathways under different metabolic conditions depends on the regulation of expression of genes, on the capacity of adipocytes to respond to external signals generated by hormones (insulin, glucagon) and by the same adipocytes or by the cells surrounding the adipocytes (macrophages) and a secretion of several adipokines by functional adipocytes (Vazgues-Vela et al 2008).

The key abnormalities that occur in the adipose tissue of 75% of severely obese people who are insulin resistant (approximately 25% are insulin sensitive) are impaired triglyceride storage and increased lipolysis by lipid droplets, mitochondrial dysfunction, inflammation, and increased oxidative and endoplasmic reticulum stress. Increased release of free fatty acids, reactive oxygen species, and inflammatory cytokines and decreased release of adiponectin from the adipocyte are thought to act on peripheral tissues causing such disorders as type 2 diabetes, atherosclerosis and non-alcoholic fatty liver disease. (Xu et al 2013). The underlying mechanism responsible for hypoadiponectinemia in the obese state is obscure. In obesity, increased fat mass results in hypoxia of adipose tissue, which increases endoplasmic reticulum stress (Su et al 2011). Autophagy, induced by endoplasmic reticulum stress, is an important mechanism underlying obesity-induced adiponectin downregulation in adipocytes (Zhou et al 2010). Obesity also induces macrophage filtration into adipocytes, resulting in a low-grade chronic inflammatory state accompanied by increased production of pro-inflammatory cytokines, such as TNFα, IL6 and IL8, which in turn can suppress adiponectin mRNA levels and its secretion from adipocytes (Su et al

2011). The BMI, the waist and hip circumference, the waist-to-hip ratio and intra-abdominal fat are inversely correlated with plasma adiponectin, with the waist-to-hip ratio having the highest correlation (Brochu-Gaudreau et al 2010).

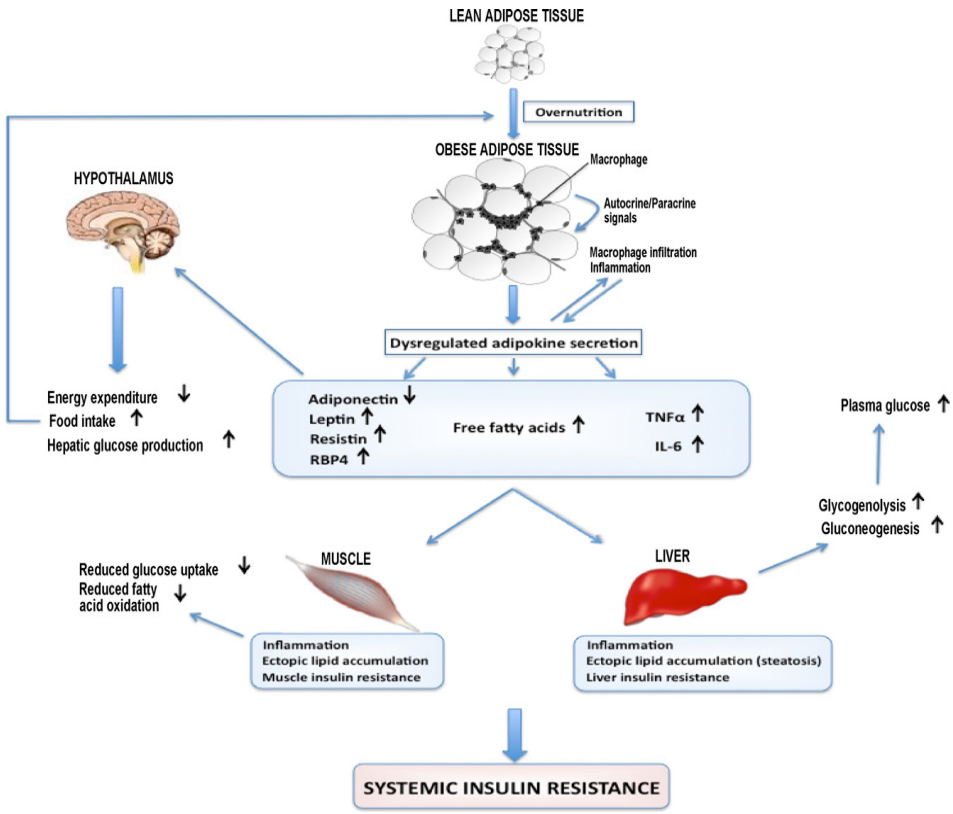

Figure 1. Obesity-induced changes in adipokine secretion and development of insulin resistance (Galic et al 2010)
Expansion of adipose tissue in obesity leads to increased macrophage infiltration and inflammation with enhanced production of pro-inflammatory cytokines such as TNFα and IL6. This is accompanied by an increased release of free fatty acids and dysregulated secretion of leptin, adiponectin, resistin and retinol binding protein-4 (RBP4). Together, these adipocyte- and macrophage-derived substances can act in a paracrine or autocrine fashion to further exacerbate adipose tissue inflammation. On the systemic level, altered adipokine secretion can lead to increased food intake and reduced energy expenditure through actions in the hypothalamus and to decreased muscle and liver insulin sensitivity through enhanced ectopic lipid deposition and inflammation.

4.5.1.3. Clinical significance of obesity

The risk of hypertension is up to five times higher among obese people than among those with normal weight. Coronary heart disease risk increases with low concentrations of HDL, as well as with high concentrations of triglycerides. The relationship between obesity and type 2 diabetes is so strong that Sims *et al* coined the term "diabesity" in the 1970s (Haslam et al 2005). Other consequences of obesity include heart failure, endocrine disorders (hyperandrogenaemia, polycystic ovary syndrome), obstructive sleep apnoea, respiratory failure, asthma, cholelithiasis, osteoarticular diseases, fatty liver, gastroesophageal reflux disease and psychological disorders such as depression. Obesity is also a risk factor for several malignant tumours, with cancers of the prostate, gallbladder, kidney and pancreas commonly affecting men and tumours of the endometrium, cervix, ovary, breast and large intestine being more prevalent in women (Gnacinska et al 2009). Obesity has been shown to decrease life expectancy by 7 years at the age of 40 years (Haslam et al 2005). The relationship between BMI and mortality can generally be illustrated by a U-shaped curve with increased mortality both in the case of lower and higher values. The causes of overweight and obesity-related increased mortality include cardiovascular disease, diabetes and kidney disease, and obesity related cancers (Dixon 2010).

4.5.1.4. Metabolically healthy obese phenotype

Being overweight or obese causes and exacerbates a large number of health problems, both independently and in association with other risk factors and diseases (Kopelman 2007).

Interestingly, not all obese individuals develop metabolic and cardiovascular disorders associated with obesity. It has been hypothesized that this is due to the preservation of normal adipose tissue architecture and function (Bluher 2009). Approximately 25% of severely obese individuals are insulin sensitive, as assessed by hyperinsulinemic-euglycemic clamps or by a homeostasis model of assessment (HOMA). Studies of bariatric surgery have shown that these individuals have higher levels of adenosine monophosphate-activated protein kinase (AMPK) and lipid droplet protein expression in adipose tissue, less oxidative stress in all of their fat depots and a decreased expression of several inflammatory genes (TNFα, interferon gamma (IFNγ), cluster of differentiation 4 (CD4)), which is more depot-selective (Xu et al 2012, Xu et al 2013).

While there exists no uniform definition of any phenotypical subtypes of obesity, the term "metabolically normal obesity" describes the absence of any overt cardiometabolic disease. In addition, the components of metabolic syndrome or inflammatory markers have also been used in categorizing subjects as metabolically normal or abnormal (Pataky et al 2010). Compared with normal weight individuals, mortality risk is increased in metabolically unhealthy obese individuals but not in metabolically healthy obese subjects, if metabolic health is defined by the homeostasis model assessment of insulin resistance (HOMA-IR) (Durward et al 2012, Hinnouho et al 2013). On the other hand, other studies have

reported similarly increased mortality risk for both metabolically healthy and unhealthy obese subjects (Stefan et al 2013). Factors that might distinguish metabolically healthy but obese individuals and metabolically abnormal obese subjects despite their similar fat mass are: insulin sensitivity, amount of ectopic fat, triglycerides level, HDL-cholesterol level, inflammation level, intima-media thickness, adiponectin level and apolipoprotein B (ApoB) level (Primeau et al 2011). Metabolically healthy obese subjects have more subcutaneous but less visceral fat mass, and lower ectopic fat deposition in the liver and in the skeletal muscle compared with metabolically unhealthy obese individuals (Stefan et al 2013). The metabolically healthy obese phenotype is characterized, besides other factors, by adiponectin levels similar to those in subjects with normal body weight (Aguilar-Salinas et al 2008, Doumatey et al 2012). Adiponectin regulates the expansion of subcutaneous adipose tissue and reduced storage of lipids in the liver, both of which being important determinants of insulin sensitivity (Stefan et al 213). Data about HMW adiponectin levels in the metabolically healthy obese phenotype is scarce. To the best of our knowledge, the only few studies have been conducted on women, where serum HMW adiponectin levels have been investigated in obese but metabolically healthy women (Bik et al 2010, Elisha et al 2010).

4.5.2. Metabolic syndrome

4.5.2.1. Factors involved in the pathogenesis of metabolic syndrome

Although obesity and insulin resistance appear to be at the core in the pathophysiology of metabolic syndrome, a number of other factors such as chronic stress, increased cellular oxidative stress, chronic activation of the immune system, activity of the renin-angiotensin-aldosterone system, microRNA-s, prenatal and early-life influences, multiple gene combinations and the contributions of cytokines, hormones and other molecules produced by adipocytes can also be involved in its pathogenesis (Simmons et al 2010, Kassi et al 2011, Hutcheson et al 2012). On the other hand, considering the data that 20% of morbidly obese individuals are metabolically healthy, and up to 40% of adults with normal weight have metabolic disorders typically associated with obesity (hypertension, dyslipidaemia, non-alcoholic fatty liver disease, type 2 diabetes), it might be assumed that obesity may not be a primary cause of metabolic syndrome but it may be rather another marker for the underlying metabolic dysfunction that potentially drives its development (Weiss et al 2013).

4.5.2.2 Insulin resistance and adipose tissue dysfunction in metabolic syndrome

The most widely accepted hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, however, it remains unclear whether this is a unifying pathophysiological mechanism (Eckel et al 2005, Cornier et al 2008). The pathophysiology of metabolic syndrome, characterized by abdominal obesity, insulin resistance and adipose tissue dysfunction, is shown in Figure 2

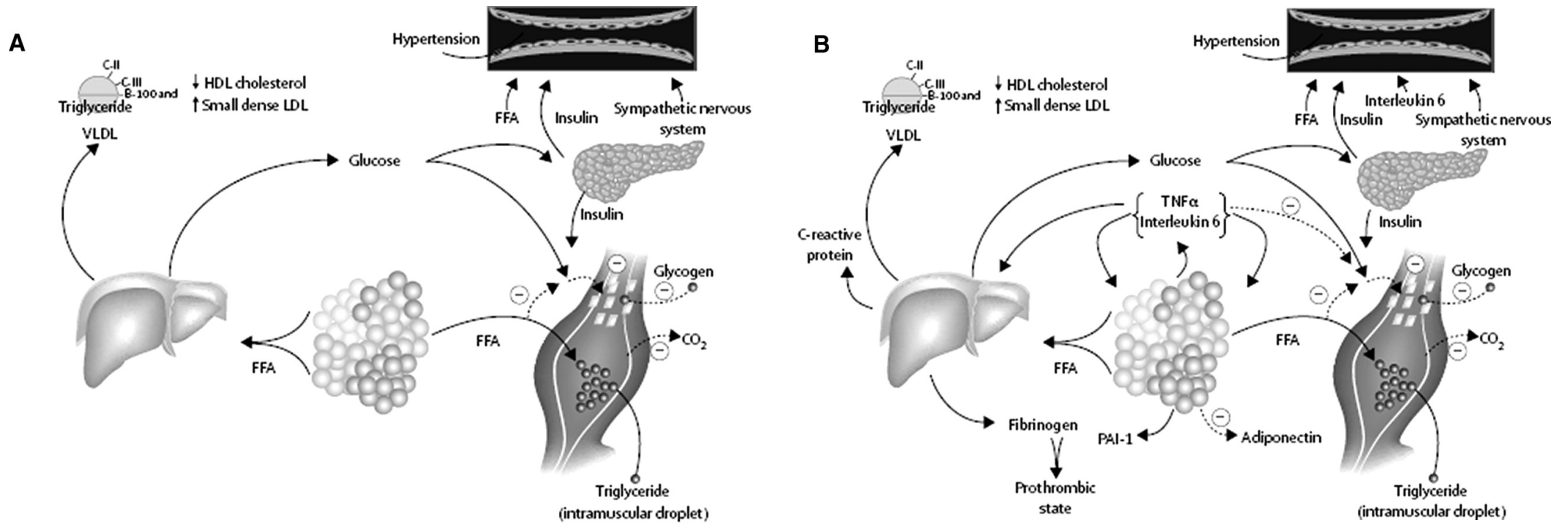

Figure 2. Pathophysiology of metabolic syndrome and insulin resistance (Eckel et al 2005)
A: Free fatty acids (FFA) are released in abundance from an expanded adipose tissue mass. In the liver, FFA result in increased production of glucose and triglycerides and secretion of VLDL. Associated lipid/lipoprotein abnormalities include reductions in HDL-C and increased density of LDL. FFA also reduce insulin sensitivity in muscle by inhibizting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation. Elevated circulating glucose and to some extent FFA increase pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system activity and may contribute to hypertension, as might increased levels of FFA.
B: Superimposed and contributory to the insulin resistance produced by excessive FFA is the paracrine and endocrine effect of the pro-inflammatory state. Produced by a variety of cells in adipose tissue, including adipocytes and monocyte-derived macrophages, the enhanced secretion of IL-6 and TNF-α among others results in more insulin resistance and lipolysis of adipose tissue triglyceride stores, resulting in increased circulating FFA. IL-6 and other cytokines also are increased in the circulation and may enhance hepatic glucose production, the production of VLDL by the liver, and insulin resistance in muscle. Cytokines and FFA also increase the production of fibrinogen and PAI-1 by the liver, complementing the overproduction of PAI-1 by adipose tissue. This results in a prothrombotic state. Reductions in the production of the antiinflammatory and insulin-sensitizing cytokine adiponectin are also associated with metabolic syndrome and insulin resistance.

(Eckel et al 2005). Insulin resistance in the liver, muscle, and adipose tissue is not only associated with the abundance of proinflammatory cytokines and relative deficiency of the anti-inflammatory cytokine adiponectin, but is a direct result of this burden (Eckel et al 2005). A strong and consistent inverse association between adiponectin and insulin resistance and inflammatory states has been established, and conversely, adiponectin levels increase when insulin sensitivity improves (after weight reduction or treatment with insulin-sensitizing drugs) (Kershaw et al 2004). Several studies have demonstrated that decreased level of adiponectin is a reliable biomarker for metabolic syndrome (Brochu-Gaudreau et al 2010) as well as an independent risk factor for non-alcoholic fatty liver disease (NAFLD) (Wang et al 2009). Furthermore, hypoadiponectinaemia is highly associated with the development of insulin resistance and type 2 diabetes (Borchu-Gaudreau et al 2010) and may be causally related to metabolic syndrome (Kassi et al 2011). On the other hand, the relationship between adiponectin and insulin action in humans is more complex than often suggested and there might be a bidirectional relationship between insulin resistance and hypoadiponectinaemia in humans (Cook et al 2010).

4.5.2.3. Clinical significance of metabolic syndrome

Individuals affected by MS have at least a fivefold increased risk of type 2 diabetes and a twofold increased risk of cardiovascular disease, the latter being independent of other classical risk factors, such as high low-density lipoprotein (LDL) cholesterol and smoking (Eckel et al 2005, Mottillo et al 2010). A meta-analysis showed that the point estimates of metabolic syndrome for cardiovascular risk were consistently higher in women vs. men (Tenenbaum et al 2011). In addition to increased risk for cardiovascular disease and type 2 diabetes, metabolic syndrome is associated with a number of other clinical conditions: NAFLD, polycystic ovary syndrome (PCOS), obstructive sleep apnoea, hypogonadism, microvascular disease, prothrombotic state, proinflammatory state (Cornier et al 2008) and certain forms of cancer (Braun et al 2011). A recent metaanalysis showed that the presence of metabolic syndrome was associated with liver, colorectal, and bladder cancer in men and with endometrial, pancreatic, breast postmenopausal, rectal, and colorectal cancer in women (Esposito et al 2012).

Metabolic syndrome may be present in a wide range of groups, from apparently healthy younger individuals, to older individuals with advanced stages of cardiovascular disease. The practical utility of MS has been greatly challenged during recent years (Borch-Johnsen et al 2010, Simmons et al 2010, Kahn et al 2005, Kahn 2008). The following concerns have been raised by critics of the concept: no unifying pathophysiological mechanism of MS has been identified as yet; the risk of cardiovascular disease conferred by the syndrome appears no greater than the sum of its parts; and the rationale for the thresholds of various diagnostic criteria is still poorly defined (Kahn et al 2005). Another shortcoming has been inclusion of individuals with established diabetes and heart

disease (Simmons et al 2010). However, it is still widely recognised that beyond age, high LDL cholesterol and other standard risk factors, MS helps identify residual vascular risk associated with insulin resistance and atherogenic dyslipidaemia (low HDL cholesterol, high triglycerides, small dense LDL cholesterol) (Tenenbaum et al 2011, Cameron et al 2009). There is general agreement that MS denotes a high life-time risk of diabetes and cardiovascular disease and it has been proposed that after exclusion of individuals with established diabetes and cardiovascular disease, MS should be considered a pre-morbid condition (Simmons et al 2010).

Metabolic syndrome is a strong risk factor for the development of cardiovascular disease in general and occlusive coronary artery disease in particular, and confers greater risk than the sum of its individual components, but the contribution of each component remains a matter of debate and might be gender-specific (Hutcheson et al 2012).

4.6. Adiponectin

4.6.1. Adiponectin synthesis, secretion and actions

Human adiponectin is a 244aminoacid/30kilodaltons protein encoded by a single gene transcript on chromosome 3q27.3 which is considered a susceptibility locus of type 2 diabetes and metabolic syndrome (Simpson et al 2010, Maeda et al 2013). Adiponectin accounts for approximately 0.01% of total plasma protein with plasma levels in the μg/ml range, around three orders of magnitude higher than leptin (Whitehead et al 2006). Adiponectin is synthesized by adipocytes as a single subunit which undergoes multimerisation to form low-molecular-weight (LMW) (trimers and hexames) and HMW (12–18-mers) multimers prior to secretion and exerts its biological effects mainly through its receptors, adiponectin receptor 1 (AdipoR1) and AdipoR2 (Antoniades et al 2009, Simpson et al 2010). The AdipoR1 is expressed ubiquiously, whereas AdipoR2 is expressed most abundantly in the liver (Rabe et al 2008). In addition to AdipoR1 and AdipoR2, the cell-surface glycoprotein T-cadherin has been identified as a receptor required for conferring the cardio-protective effects of adiponectin (Hui et al 2012). In plasma, adiponectin circulates as a LMW trimer, a middle-molecular-weight (MMW) hexamer, and HMW 12- to 18-mer, which have different target tissues and/or differing biological effects (Wang et al 2008, Rabe et al 2008, Simpson et al 2010). The physiological function of adiponectin has been clarified and mainly investigated by using adiponectin knockout (Adipo-KO) mice (Maeda et al 2013). Activation of AMPK is the central mechanism of the biological effects of adiponectin (Shetty et al 2009, Wang et al 2008). The AdipoR1 and AdipoR2 also mediate adiponectin-evoked activation of peroxisome-proliferator activated receptor alpha (PPARα) and P38 mitogen-activated protein (MAP) kinase in the liver, sceletal muscle and endothelial cells (Hui et al 2012). Adiponectin has anti-inflammatory actions in a variety of tissues: direct effects on monocyte/

macrophages, endothelial cells, hepatic and muscle cells plus indirect effects via inhibition of TNFα production and action (Whitehead et al 2006) and suppression of IL6 expression (Rabe et al 2008). Adiponectin increases nitric oxide (NO) production and/or ameliorates oxidized LDL (oxLDL)-induced suppression of endothelial NO synthase (eNOS) activity, and loss of adiponectin is associated with impaired endothelium-dependent vasorelaxation. Adiponectin also inhibits one of the initial steps in atherogenesis, i.e. TNFα-stimulated adherence of monocytes to cultured human endothelial cells, and affects plaque formation and stability (Matsuzawa 2005). Adiponectin regulates glucose homeostasis through suppression of hepatic gluconeogenesis, stimulation of fatty acid oxidation in the liver and skeletal muscle and glucose uptake in skeletal muscle, stimulation of insulin secretion and modulation of food intake and energy expenditure (Rabe et al 2008). Adiponectin is considered to have anticarcinogenic effects, being a negative regulator of angiogenesis and having anti-inflammatory properties (Braun et al 2011). Recent studies also indicate that adiponectin is directly involved in bone-mass regulation, revealing both positive and negative correlations (Shetty et al 2009). The actions of adiponectin in major target tissues are shown in Figure 3 (Simpson et al 2010).

Numerous studies have indicated that the HMW form of adiponectin is its most active form (Hara et al 2006, Hajer et al 2008, Mattu et al 2013) which also mediates the insulin-sensitizing and cardiovascular protective effects of adiponectin (Hui et al 2012). Due to its anti-inflammatory, anti-atherogenic, anti-diabetic and cardioprotective effects and promotion of efficient endothelial function, adiponectin is termed as “beneficial” adipocytokine (Mattu et al 2013).

Both genetic and environmental factors affect circulating adiponectin levels (Kishida et al 2011). Single nucleotide polymorphisms (SNPs) present in the adiponectin gene are independently associated with one or more aspects of metabolic syndrome, including type 2 diabetes, increased BMI, waist circumference, dyslipidaemia, altered blood pressure and coronary artery diseases (Shetty et al 2009, Su et al 2011). Adiponectin gene transcription is upregulated by peroxisome proliferator activator receptor gamma (PPARγ) and downregulated in the adverse environment of chronic low-grade inflammation, oxidative stress, and endoplasmic reticulum stress that is associated with obesity (Phillips et al 2010). Many existing drugs have been found to increase adiponectin levels, such as thiazolidinediones, statins, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), fenofibrate, niacin, acarbose, glimepiride, androgen blockers and rimonabant (withdrawn from the market due to psychiatric side effects) (Phillips et al 2010). Adiponectin levels are also hormonally regulated: testosterone selectively decreases the circulating levels of HMW adiponectin, triggering lower levels of adiponectin in men compared to women (Wang et al 2008, Shetty et al 2009). There are also ethnic differences in adiponectin levels: plasma total and HMW adiponectin concentrations were lower in Chinese and South Asians compared with Canadian aborigines and Europeans (Sulistyoningrum et al 2013).

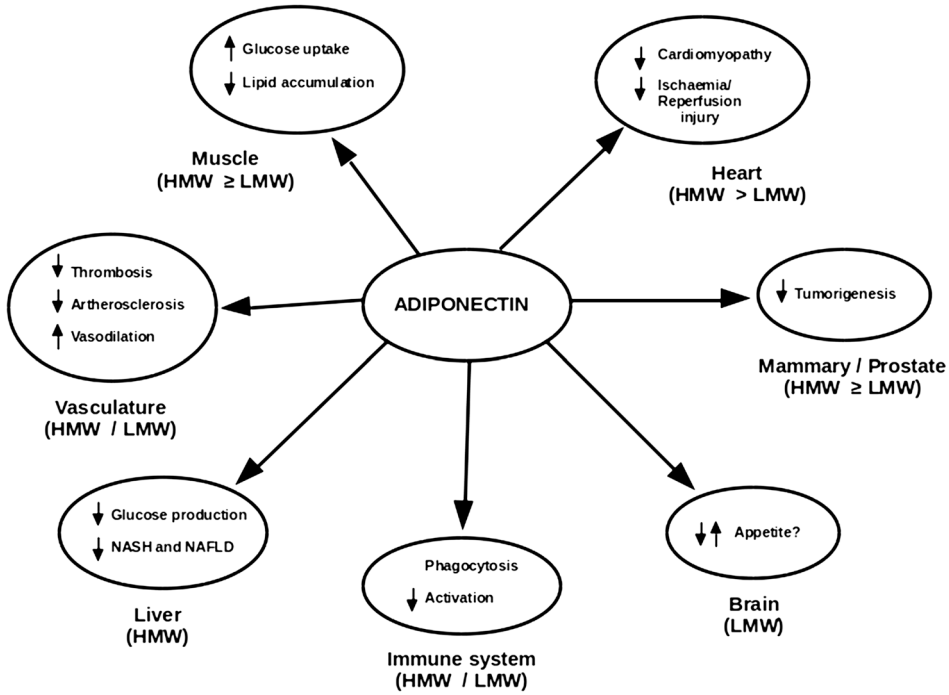

Figure 3. Actions of adiponectin in major target tissues.
NAFLD: non-alcoholic liver disease; NASH: non-alcoholic steatohepatitis.

In obese subjects, weight loss and increased physical activity are associated with an increase in plasma adiponectin (Matsuzawa 2005). Specifically, a net weight loss larger than 10% of initial body weight seemed necessary for long-term combined improvement of adiponectin, high sensitive-C reactive protein and fibrinogen levels (Madsen et al 2008). Marked elevation of adiponectin is seen in humans in chronic calorie deficiency (anorexia nervosa) (Cook et al 2010).

In conclusion, low adiponectin level is a biomarker of a number of disease conditions (obesity, insulin resistance and type 2 diabetes, cardiovascular diseases, dyslipidaemia, hypertension, metabolic syndrome). At the same time, adiponectin itself mediates a range of anti-inflammatory, anti-atherosclerotic and antidiabetic effects, therefore being closely involved in the pathogenesis of diabetes and cardiovascular diseases (Matsuzawa 2005, Su et al 2011). In addition, adiponectin may provide a mechanism by which obesity and insulin resistance are causally associated with cancer risk and its poor prognosis (Matsuzawa 2005).

4.6.2. Gender difference in adiponectin levels

Previous studies have convincingly shown that males have significantly lower levels of adiponectin than females (Nishizawa et al 2002, Rathmann et al 2007,

Wang et al 2008, Ahonen et al 2009). Xu *et al* have found that the concentration of HMW adiponectin in females was significantly higher than that in males, whereas there were no gender difference for the other two forms. Therefore, selective inhibition of HMW adiponectin by testosterone might contribute to the sex dimorphism of adiponectin levels and could partly explain why men have higher risk for insulin resistance and atherosclerosis than women (Xu et al 2005). Several lines of evidence suggest that both androgens and oestrogens play negative roles in the production of adiponectin. Neonatal castration of male rats results in adiponectin levels similar to those observed in females and ovariectomy in adult women also increases circulating adiponectin levels (Whitehead et al 2006).

4.6.3. Adiponectin, inflammation and metabolic risk factors: consensus and controversy

Among various adipokines, adiponectin stands out due to its abundant expression in adipose tissue and inverse relationship with insulin resistance (Rabe et al 2008), metabolic syndrome (Rabe et al 2008, Hirose et al 2010) and type 2 diabetes (Snijder et al 2006, Jalovaara et al 2008, Rabe et al 2008, Cook et al 2010, Zhu et al 2010). Serum HMW adiponectin values are inversely correlated with presence of metabolic syndrome in both genders (Hara et al 2006, Eglit et al 2013). The HMW adiponectin is the most active form of the hormone, and has a better predictive power compared to total adiponectin for glucose intolerance, insulin resistance and MS (Fisher et al 2005, Hara et al 2006, Rabe et al 2008, Cook et al 2010). The HMW adiponectin is inversely associated with triglycerides, obesity and fasting glucose, and positively associated with HDL cholesterol (Liu et al 2007, Tabara et al 2008, Kawamoto et al 2011, Yu et al 2011). The relationship between HMW adiponectin and blood pressure has varied between different studies as well as between the genders (Liu et al 2007, Tabara et al 2008, Kawamoto et al 2011b, Yu et al 2011). This calls for more detailed subtype analyses of the association between adiponectin, gender and metabolic risk factors.

The most recent studies about associations between HMW adiponectin and MS come mainly from Asia (Liu et al 2007, Lee et al 2009, Kawamoto et al 2011, Yu et al 2011) and from the United States (Devaraj et al 2008). The SWAN study from the United States showed significant racial-ethnic differences in circulating adipokine levels. Women of Caucasian origin had higher levels of total and HMW adiponectin compared with women of African American, Chinese and Japanese origin (Khan et al 2012). Furthermore, the relationship between plasma HMW adiponectin and HOMA-IR is influenced by ethnicity to a greater degree for Chinese and South Asians compared with Europeans (Sulistyoningrum et al 2013). However, no data is available about associations between HMW adiponectin and metabolic syndrome in Europe. There is a clear gender difference in HMW adiponectin levels: women have significantly higher HMW adiponectin levels compared with men (Nishizawa et

al 2002). However, data about whether this gender dimorphism has any consequences in cardiometabolic conditions in females versus males is scanty. A recent study from Finland investigating subjects with both metabolic syndrome and elevated blood pressure showed that absolute differences in total adiponectin levels between subjects with and without metabolic syndrome were greater for women than for men (Ahonen et al 2009). Several studies have shown that the inflammation characterized by elevated C-reactive protein (CRP), predicted development of metabolic syndrome more accurately in women than in men. Furthermore, the association between elevated CRP and cardiovascular events was stronger for women than for men and the increase in cardiovascular risk accompanied by the appearance of diabetes was relatively greater for women than for men as reported in several studies (Regitz-Zagrosek et al 2006). In pharmacologically untreated subjects, the leptin/adiponectin ratio is the main factor associated with metabolic syndrome in men, while adiponectin alone appears to be a protective factor in women (Cicero et al 2011). The Dutch Hoorn Study demonstrated that the relationship of high total adiponectin level with lower risk of impaired glucose metabolism and type 2 diabetes was stronger among women than among men in a group of 50–70-years-old subjects (Snijder et al 2006). However, no gender difference was found in associations between total adiponectin and cardiovascular risk factors in German subjects aged 55–74 years (Cooperative Health Research in the Region of Augsburg (KORA) Survey 2000) (Rathmann et al 2007). In subjects with a normal waist circumference, the prevalence of visceral fat obesity (defined as the area of visceral adipose tissue larger than 100 cm^2 by CT) is lower and the expression of adiponectin and its receptor is higher in female subjects compared with male subjects (He et al 2010). Whether the higher expression of adiponectin and its receptor constitutes a mechanism for protecting female subjects from developing visceral fat obesity requires further investigation (He et al 2010).

Controversial issues. A substantial amount of coherent data has generated the following paradigm: obesity is associated with inflammation in adipose tissue, proinflammatory factors suppress adiponectin production, low levels of adiponectin increase insulin resistance and risk of cardiovascular disease and low levels of adiponectin promote inflammation, thus generating a self-sustaining inflammatory loop (Fantuzzi 2008). On the other hand, adiponectin levels have recently been shown to be increased in many chronic inflammatory and autoimmune diseases such as type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, chronic systolic heart failure (contrary to the decrease in adiponectin levels in obesity related heart failure) and hypertrophic cardiomyopathy associated with diastolic dysfunction (Aprahamian et al 2011). This data might suggest that the paradigm "inflammation→low adiponectin→more inflammation", currently accepted in the context of obesity, metabolic syndrome, type 2 diabetes and cardiovascular disease, does not apply to classic chronic inflammatory conditions, in which increased adipose tissue mass does not likely play a pathogenic role (Fantuzzi 2008). High adiponectin levels correlating with increased mortality in patients

with heart failure might be an expression of protective counter-regulatory measure to prevent further damage (Shetty et al 2009). Another opinion is that in severe heart failure elevated levels of adiponectin may just reflect the hypercatabolic state and therefore adiponectin levels are increased in heart failure only in the presence of cachexia (Antoniades et al 2009). In addition, adiponectin concentration correlates positively with renal dysfunction, but it is unclear whether increased adiponectin levels in such a situation have a causative or reactive (and protective) role (Shetty et al 2009). More research into the role and regulation of adiponectin in inflammation and autoimmunity is clearly necessary (Fantuzzi 2008, Shetty et al 2009).

5. STUDY RATIONALE

The prevalences of diabetes, impaired glucose regulation and metabolic syndrome have not been previously studied in Estonia. The prevalence of obesity has been estimated on the basis of self-reported data obtained by using a postal questionnaire survey, and no population-based study has been conducted. Data on gender-specific associations between adiponectin (especially HMW adiponectin) levels and cardiometabolic risk factors is so far rather limited. Data about HMW adiponectin levels in metabolically healthy obese subjects is also scarce.

6. AIMS OF THE STUDY

1. To estimate the prevalence of obesity, impaired glucose regulation and metabolic syndrome in Estonian adult population.
2. To analyse associations between metabolic syndrome and insulin resistance.
3. To describe gender-specific associations between metabolic syndrome and HMW adiponectin level.
4. To analyse gender-specific associations between HMW adiponectin level and metabolic risk factors.
5. To compare HMW adiponectin levels in metabolically healthy and unhealthy subjects.

7. SUBJECTS AND METHODS

A population-based, cross-sectional, multicentre study was conducted between November 2008 and May 2009 in three different counties (Viljandi, Põlva and Tartu) of Estonia. The study population consisted of randomly selected adults, aged 20 to 74 years, from four general practices (2 from the Viljandi County). The study participants were representative of the general Estonian population in terms of age and gender. An invitation letter about the study was sent to each participant. The total response rate was 53.2 percent, resulting in a total study population of 495 subjects (Table 1).

Table 1. The age- and gender specific structure of the study population

Age-group (years)	Men (n)	Women (n)	Total (n)
20–44	105	116	221
45–60	64	99	163
61–74	45	66	111
Total	**214**	**281**	**495**

On the day of the study, subjects visited their general practitioners (GPs) in the morning between 8 a.m. and 11 a.m. after an overnight fast (lasting at least 10 hours). An informed consent form was signed, and blood pressure, waist circumference, height and weight were measured in participants wearing their indoor clothes without shoes. Blood pressure was measured using a mercury sphygmomanometer after the patient had been sitting for at least five minutes. The mean of three consecutive measurements was used for analysis, with at least a three-minute interval between each measurement. A face-to-face clinical interview was conducted to assess the presence of other medical conditions and cardiovascular risk factors. A standard OGTT (WHO 1999) was conducted with Glycodyn® solution (Biofile Ltd, Turku, Finland), except for the subjects with known diabetes mellitus. Plasma glucose was measured by the hexokinase method. Total cholesterol, HDL cholesterol, and triglycerides were measured using an enzymatic colorimetric assay (COBAS INTEGRA 800 plus analyzer, Roche, Basel, Switzerland). Plasma insulin was measured using a chemiluminescent assay (Immulite 2000 analyser, Siemens Healthcare Diagnostics, Deerfield, IL, USA). Plasma fasting HMW adiponectin was measured subsequently in 458 subjects (191 men) from plasma samples that had been stored at -80Cº for a maximum of 2.5 years and had never been thawed. The HMW adiponectin was detected by an Adiponectin (Multimetric) enzyme-linked immunosorbent assay (ELISA) (ALPCO Diagnostics, Salem, NH, USA), using an automatic ELISA Triturus analyser (Grifols International, Barcelona, Spain). The intra-assay coefficient of variation for the HMW adiponectin

ELISA was 4.8 percent (n=9), and the interassay coefficient of variation was 6.9 percent (n=7).

The subjects were categorized as normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI≥25.0 kg/m^2) and obese (BMI ≥30.0 kg/m^2) (World Health Organization 2000). Impaired glucose regulation was diagnosed according to the WHO criteria (World Health Organization 2006). Insulin resistance (IR) was estimated using homeostasis model assessment: HOMA-IR = fasting glucose (mmol/l) x fasting insulin (mU/l)/22.5 (Wallace et al 2004). The IR was defined as the upper quartile of HOMA-IR for the whole study group (exempting subjects with previously known diabetes mellitus). The threshold for the whole study group was 1.92 (2.04 and 1.82 for men and women, respectively).

Metabolic syndrome was diagnosed on the basis of at least three of the following NCEP ATP III criteria (Grundy et al 2005): waist circumference ≥102 cm in men and ≥88 cm in women, blood pressure ≥130/85 mmHg or taking antihypertensive medication, fasting glucose ≥5.6 mmol/l or previously diagnosed diabetes, triglycerides ≥1.7 mmol/l or taking lipid-regulating medication, high-density lipoprotein (HDL) cholesterol <1.03 mmol/l in men and <1.30 mmol/l in women or drug treatment for reduced HDL cholesterol. For subgroup analysis, all subjects with MS were divided into two groups: subjects without previously diagnosed diabetes, dyslipidaemia or hypertension (pre-morbid subgroup) and subjects with a previous diagnosis of any of the above conditions (morbid subgroup).

Metabolically healthy subjects were defined as subjects without impaired glucose regulation, without dyslipidaemia (triglycerides ≥ 1.7 mmol/L or HDL cholesterol < 1.3 mmol/L in women or HDL cholesterol < 1.03 mmol/l in men or lipid-lowering treatment), without hypertension (blood pressure ≥130/80 mmHg or on antihypertensive treatment) and without insulin resistance. “Metabolically unhealthy” was defined as having at least one of the above-mentioned four risk factors. The study was approved by the University of Tartu Ethics Review Committee on Human Research.

Statistical analysis. Due to the slight underrepresentation of younger age-groups (20–39 years), the prevalences of impaired glucose regulation, metabolic syndrome and obesity were weighted to the Estonian 20–74-year-old population (estimated in 2009). The prevalences of impaired glucose regulation, metabolic syndrome and obesity were presented as a proportion with 95% confidence intervals (95% CI-s). The chi-square test (with Bonferroni correction) was used for multiple comparison of prevalence between three age-groups. Descriptive statistics as medians and interquartile ranges, or as means and standard deviations were calculated for the continuous variables. The Mann-Whitney U test was used for comparisons between different groups. Spearman partial correlations coefficients were used to estimate associations between HMW adiponectin and metabolic risk factors. Linear regression analysis with logarithmed HMW adiponectin levels was used for trend analysis over continuous age (adjusted for gender) and for examining association between HMW adiponectin

and gender (adjusted for waist circumference, BMI and use of diabetes, antihypertensive and lipid-lowering medicines). Multiple logistic regression analysis was used to calculate the odd ratios (ORs) and the 95 percent confidence intervals (CIs) for MS risk factors. Receiver operating characteristic (ROC) curves were generated to compare the ability of HMW adiponectin and HOMA-IR to discriminate between subjects with and without MS. The nonparametric approach was used for comparing the areas under the ROC curves (AUROC). P values were considered statistically significant at the 0.05 level. Statistical analysis was performed using the R software version 2.15.3 (R Core Team 2013).

8. RESULTS

8.1. Prevalence of obesity, impaired glucose regulation and metabolic syndrome among the Estonian adult population

8.1.1. Prevalence of overweight and obesity (Paper I)

The prevalence of obesity weighted for the Estonian population in 2009 was 32% (29% for men and 34% for women). The prevalence of obesity was significantly higher in the oldest age group compared with the youngest age group: 48% vs. 27%, respectively, p=0.0002. There was no significant gender difference in the prevalence of obesity (Table 1). The prevalence of being overweight or obese (defined as BMI ≥25) was 67% (95% CI 62−71) in the study group, with 72% (95% CI 66−78) for men and 63% (95% CI 57−68) for women.

8.1.2. Prevalence of impaired glucose regulation (Paper II)

The prevalence of diabetes weighted for the Estonian population in 2009 was 7%, 8% for men and 7% for women. The prevalence of diabetes increased with age. Nearly half (49%) of the diabetes cases had been undiagnosed until the subject was assessed in our study. The prevalence of IFG and IGT weighted for the Estonian population in 2009 was 5% and 8%, respectively. Taken together, our results showed that 20% of the Estonian adult population had impaired glucose regulation (Table 1).

8.1.3. Prevalence of metabolic syndrome (Paper III)

The prevalence of MS weighted for the Estonian population in 2009 was 26%, 29% for men and 24% for women. The prevalence of MS increased significantly with age. The prevalence was significantly (p=0.02) higher for men when compared with women in the youngest age group only, and there were no gender-specific differences in the prevalence in the middle-aged and older age groups (Table 1).

8.2. Associations between metabolic syndrome and insulin resistance (Paper III)

8.2.1. Characteristics of subjects with metabolic syndrome

Most of the subjects with MS had 3 components of the syndrome (56%), 32% had 4 and 12% had all 5 components. Arterial hypertension (94%), abdominal obesity (91%), and impaired glucose metabolism (71%) were the most common abnormalities in subjects of both sexes.

8.2.2. Characteristics of the subjects in the premorbid and morbid subgroups with metabolic syndrome

The subjects of the pre-morbid subgroup were significantly younger, had lower systolic blood-pressure, lower BMI and smaller waist circumference (for BMI and waist, only the difference between the pre-morbid and the morbid men reached statistical significance). The HOMA-IR values and lipid levels did not differ between the morbid and pre-morbid subgroup (Table 3).

8.2.3. Associations between metabolic syndrome and insulin resistance

The prevalence of insulin resistance (defined as the top quartile of HOMA-IR for the whole study group excluding subjects with previously known diabetes) among subjects with and without MS was 62% (95% CI 54−70) and 12% (95% CI 9−16), respectively ($p<0.001$). The prevalence of insulin resistance among subjects with MS in the pre-morbid and morbid subgroups did not differ, being 59% (95% CI 44–72%) and 64% (95% CI 53–74%), respectively ($p=0.64$).

8.3. Gender differences in serum HMW adiponectin levels in metabolic syndrome (Paper IV)

8.3.1. Age- and gender-specific levels of HMW adiponectin among the Estonian adult population

The median HMW adiponectin level (μg/ml) was significantly higher ($p<0.001$) in women than in men (4.6, 2.9−6.5 vs. 2.5, 1.5−3.8; median, interquartile range, respectively). This gender difference in HMW adiponectin levels remained significant also after adjustment for waist circumference, BMI and use of diabetes, antihypertensive and lipid-lowering medicines. The median HMW adiponectin levels in 10-year age groups, forming the whole study population, showed an increase in the older age groups for both genders. There was significant positive association between HMW adiponectin and age in trend analysis ($p=0.01$) (Figure 1).

8.3.2. Associations between HMW adiponectin and metabolic syndrome and insulin resistance

The median (interquartile range) HMW adiponectin level was significantly lower for both genders among subjects with MS compared to those without MS: 2.1 (1.3−3.0) vs. 2.8 (1.7−4.3) in men ($p=0.002$); and 3.1 (2.1−4.8) vs. 5.1 (3.5−6.9) in women ($p<0.001$). The median (interquartile range) HOMA-IR was significantly higher in both genders among subjects with MS compared to those without MS: 2.53 (1.54−3.98) vs. 0.76 (0.47−1.27) for men ($p<0.001$); and 2.45

(1.45−3.52) vs. 0.89 (0.49−1.37) for women ($p<0.001$). The median (interquartile range) HMW adiponectin level was significantly lower in both genders in insulin-resistant subjects compared with those without insulin resistance: 1.9 (0.9−2.8) vs. 2.8 (1.7−4.2) in men ($p<0.001$) and 3.0 (2.1−4.7) vs. 5.1 (3.5−6.8) in women ($p<0.001$).

In multiple logistic regression analysis HMW adiponectin remained significantly inversely related to MS only for women, even after controlling for age, BMI, and HOMA-IR (Table 2).

The predictive value of HMW adiponectin for MS was significantly lower than that of HOMA-IR. The crude AUROC for HMW adiponectin and HOMA-IR were 0.64 vs. 0.864 in men ($p<0.001$) and 0.702 vs. 0.839 in women ($p=0.0008$) (Figure 2).

After adjustment for age and BMI, the predictive value of HMW adiponectin remained lower than that of HOMA-IR only for men, but became equal with that of HOMA-IR for women. The AUROC for HMW adiponectin and HOMA-IR for men were 0.833 vs. 0.88 ($p=0.02$) and 0.897 vs. 0.907 for women ($p=0.5$) (Figure 3).

8.4. Associations between HMW adiponectin levels and metabolic risk factors (Paper I)

We assessed correlations between HMW adiponectin and metabolic risk factors for the whole study group after adjusting for age. For both genders, HMW adiponectin was positively correlated with HDL cholesterol, and negatively correlated with triglycerides, waist circumference, BMI, HOMA-IR, fasting insulin and fasting glucose. For women only, a significant negative correlation was found between HMW adiponectin and systolic and diastolic blood pressure as well as 2-hour glucose levels on OGTT (Table 2).

8.5. HMW adiponectin levels in metabolically healthy and unhealthy subjects (Paper I)

Among the whole study group, 33% of the subjects were metabolically healthy (151/458 subjects, whereby their prevalence was 27% for men and 37% for women, *p*-value=0.03). The percentage of the study subjects who used antihypertensive, lipid-lowering and antidiabetic treatment was 26.6, 3.9 and 4.1%, respectively, and there was no gender difference. We did not find significant associations between HMW adiponectin level and smoking or between HMW adiponectin level and alcohol consumption.The correlation between HMW adiponectin and metabolic risk factors for men was driven exclusively by the metabolically unhealthy subgroup. For women too, the metabolically unhealthy subgroup again drove largely this correlation. However, also metabolically healthy women showed correlations between HMW adiponectin and HDL

cholesterol, triglycerides and insulin resistance (Table 2). Moreover, metabolically healthy women showed substantially higher HMW adiponectin levels compared with metabolically unhealthy women. For men we did not find a significant difference in the median HMW adiponectin levels between metabolically healthy and unhealthy subjects. Metabolically healthy subjects were significantly younger and had significantly lower HOMA-IR, waist circumference and BMI compared with metabolically unhealthy subjects in both genders (Table 3).

8.6. Comparison of HMW adiponectin levels between metabolically healthy and unhealthy overweight/obese subjects (Paper I)

Among the overweight or obese subjects (BMI≥25), we compared metabolically healthy and unhealthy subjects. In both genders, metabolically healthy subjects were significantly younger and had a significantly smaller waist circumference and lower HOMA-IR. The HOMA-IR level in metabolically healthy overweight/obese subjects was comparable to that in subjects with a normal BMI. Among the women, metabolically healthy overweight/obese subjects had higher HMW adiponectin levels compared with metabolically unhealthy overweigh/ obese women. The HMW adiponectin levels in metabolically healthy overweight/obese women were comparable to those in women with a normal BMI (Table 4).

Among obese subjects, 12% were metabolically healthy (19/158 subjects, whereby the prevalence was 11% for men (6/57 subjects) and 13% for women (13/101 subjects), *p*-value=0.9). Median HMW adiponectin levels for metabolically healthy obese and metabolically unhealthy obese subjects were 3.338 vs. 1.957 (p=0.04) for men, and 5.079 vs 3.091 μg/ml (p=0.1) for women. This suggests that for obese subjects of both genders, HMW adiponectin levels in metabolically healthy subjects are comparable to those in subjects with normal weight. Metabolically healthy obese subjects were significantly less insulin resistant than metabolically unhealthy obese subjects of both genders. There was no difference in mean age between metabolically healthy and unhealthy obese subjects of both genders (Table 4).

9. DISCUSSION

9.1. Prevalence of obesity, impaired glucose regulation and metabolic syndrome

9.1.1. Analysis of the study population

The study population is truly representative of the general Estonian population (1.34 million inhabitants in 2009). The sample of 495 subjects represented a mixed urban-rural population of Estonia and it was randomly drawn from the patient registers of four general practice centres. It is important to note that every resident of Estonia is in a general practitioner register either after patient´s personal choice or according to his/her address. All four general practitioner centres were situated in small residential areas and were attended by most inhabitants according to the population register. Due to the slight underrepresentation in the younger age group (20–39 years), the prevalences of obesity, impaired glucose regulation and metabolic syndrome were weighted for the Estonian adult population (estimated in 2009).

9.1.2. Prevalence of overweight and obesity

In this population-based, multicentre, cross-sectional study we found that the prevalence of obesity among Estonian adults aged 20–74 was significantly higher than previously estimated: 32% (29% for men and 34% for women, weighted for the Estonian population in 2009). In comparison, the prevalence estimated by self-reported data in 2008 among subjects aged 16–64 years was just 17.5% for men and 18.0% for women (Tekkel et al 2009). The prevalence of obesity is known to increase with age and the subjects of our study group were slightly older. However, this slight shift in demographics is insufficient to explain this nearly twofold difference. Previous studies have shown that the prevalence of being overweight is higher if calculated from measured values as opposed to self-reported values (Kuczmarski et al 2001). Furthermore, non-responders to self-reported body weight questions in health questionnaires are more likely to be obese (Nyholm et al 2008). These factors may partially explain why self-report methods underestimate the prevalence of obesity.

Recent European studies, using objective data, have assessed the prevalence of obesity as being of same magnitude as we have currently found for Estonia: for example in Latvia 26% for men and 33% for women (Erglis et al 2012), in Albania 24% for men and 36% for women (Spahija et al 2012) and in Croatia 26% for men and 34% for women (Poljicanin et al 2012). The high prevalence of overweight and obesity (defined as BMI $\geq$25) in Estonia (67%) is also comparable to recent prevalence rates from Latvia (68%) (Erglis et al 2012). Our finding has important implications for public health policy in Estonia. To date, many practitioners had believed that Estonia was more or less spared the global obesity epidemic. Our data presents contrary evidence, according to

which the problem of obesity is as serious in Estonia as it is in other Western countries, and hence this issue deserves increasing attention in the sphere of public health policy.

9.1.3. Prevalence of impaired glucose regulation

The prevalence of diabetes among adults in Estonia (7%) is comparable to that in other European countries (Shaw et al 2010). The current study addressed the knowledge gap in the prevalence of diabetes and impaired glucose regulation among adults in Estonia, providing more accurate estimates on the prevalence of these disorders than those predicted previously on the basis of extrapolated data.

9.1.4. Prevalence of metabolic syndrome

We estimated the age- and gender-specific prevalence of MS for 20–74-year-old Estonian adults according to NCEP ATP III criteria. A recent joint scientific statement issued by different international organisations agreed on the threshold values for most of the components of MS, with the exception of waist circumference, for abdominal obesity. The IDF criteria define abdominal obesity at a lower threshold (≥ 94 cm in men and ≥ 80 cm in women) than the NCEP ATP III criteria (Alberti et al 2009). We chose to use the NCEP ATP III criteria for prevalence estimations as studies from Europe and the United States generally use higher thresholds for waist circumference (Alberti et al 2009). Moreover, a recent meta-analysis of nearly one million patients convincingly demonstrated a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality for individuals diagnosed with MS according to the NCEP ATP III criteria (Mottillo et al 2010), adding further credibility to the practical application of the NCEP ATP III criteria.

In our study, we found 28% of subjects to be affected by MS while the weighted prevalence rate for the general population was 26%. In comparison with the prevalence of MS in other countries, the DECODE study including pooled data from nine European population-based cohorts showed higher average prevalence of MS: 32.2% and 28.5% for men and women, respectively (Qiao 2006). However, the DECODE study population was notably older (30–89 years). More recent studies from Europe that have estimated the prevalence according to NCEP ATP III in age groups comparable to those of our study population have shown quite comparable results: 25.9% in Norway (Hildrum et al 2007), 28.8% in Turkey (Gündogan et al 2009), and 24.7% in Luxembourg (Alkerwi et al 2011). Furthermore, our estimates of the prevalence of diabetes (7%) and impaired glucose tolerance (8%) in Estonia are also comparable to those found in other developed countries (Eglit et al 2011). Thus, the prevalence of metabolic syndrome in Estonia appears to be similar to that in the rest of the developed regions.

MS was more common in men than in the women of the younger age group only, followed by an equalisation of the gender-specific prevalence in the middle age group and thereafter. These gender-specific differences in Estonia are generally comparable to the patterns described from other populations (Cornier et al 2008). However, the difference in the prevalence between the men (26%) and the women (13%) in the youngest age group is more pronounced compared with data, for example, from the USA (Cornier et al 2008). Our neighbouring country Finland recently reported a similar twofold increase in the prevalence of MS among 24–39-year-old men in comparison with women (Mattsson et al 2007). These regional observations are particularly noteworthy given that of all countries of the European Union, gender differences in life expectancy are also the greatest in the Baltic States (Eurostat 2010). Our findings suggest that the distribution of MS between young men and women may contribute to the large gender related differences in life expectancy in the North-East of Europe, as life expectancy for these young men may be reduced by subsequent development of cardiovascular disease and diabetes. Further studies could establish whether the high prevalence of MS for young men in the North-East of Europe is due to genetic vulnerability, environmental influence, or an interaction between these two.

9.2. Associations between metabolic syndrome and insulin resistance

There is general agreement that MS denotes a high life-time risk of diabetes and cardiovascular disease and it has been proposed that after exclusion of individuals with established diabetes and cardiovascular disease MS should be considered a pre-morbid condition (Simmons et al 2010). In addition, a recently coined term “Nascent MS” denotes subjects with MS but without the confounding presence of diabetes and/or cardiovascular diseases (Jialal et al 2012). Nascent MS is associated with increased oxidative stress, increased levels of adipocytokines and decreased levels of adiponectin, which are related to insulin resistance in inflammation (Jialal et al 2012, Bremer et al 2013).

In the context of considering MS a pre-morbid condition, we divided the study subjects with metabolic syndrome in to the pre-morbid and morbid subgroups. Comparison of these groups showed that, as expected, pre-morbid individuals were significantly younger than morbid subjects, and male subjects were significantly less obese (regarding both waist circumference and BMI). Despite these differences, pre-morbid subjects proved to be as insulin resistant as morbid subjects as estimated by HOMA-IR. This may indicate that insulin resistance is a hallmark of MS already in the early stage of this disorder. However, insulin resistance of the same magnitude in the premorbid and morbid subgroups with MS should be interpreted with caution, due to the therapeutic effects of lifestyle and medical interventions on alleviating insulin resistance in the morbid subgroup. Elevations of insulin concentration have been shown to

precede the development of diabetes and multiple metabolic disorders in large prospective studies (Haffner et al 1992, Tabak et al 2009). Moreover, insulin resistance *per se* is a well established independent predictor of cardiovascular disease (Jeppesen et al 2007, Tenenbaum et al 2007). In line with previous studies (Cheal et al 2004, Stern et al 2005), our results support the conclusion that a high proportion of insulin resistant subjects, both apparently healthy individuals and those with established cardiometabolic abnormalities, can be identified by simple measurements defining MS. Therefore, MS seems to remain a useful practical tool for early identification of apparently healthy individuals at a considerable risk of cardiovascular disease and diabetes.

9.3. Gender difference in serum HMW adiponectin levels in metabolic syndrome

In line with previous studies (Nishizawa et al 2002, Wang et al 2008), our results confirmed a clear gender difference in adiponectin levels: women had significantly higher HMW adiponectin level compared with men. Considering the gender difference in HMW adiponectin levels, we made a gender-specific logistic regression analysis to determine the association between HMW adiponectin and MS and found that after adjustment for age, BMI and HOMA-IR, HMW adiponectin remained significantly associated with MS only for women. Similarly, a recent study from Finland in subjects with elevated blood pressure also demonstrated that after adjustment for BMI, the association between total adiponectin and presence of MS was statistically significant for women but not for men (Ahonen et al 2009). In addition, we found that after adjusting for age and BMI, HOMA-IR remained a better predictor of MS compared with HMW adiponectin for men, while there was no difference in this respect for women (estimated by AUROC). Therefore, these results demonstrate stronger relationship between HMW adiponectin and MS for women. Associations between HMW adiponectin levels and presence of MS have been studied previously in Japanese (Hirose et al 2010, Kawamoto et al 2011), Caucasian American (Devaraj et al 2008) Japanese American (Nakashima et al 2011), Thai (Liu et al 2007), Korean (Lee et al 2009), and Chinese subjects (Yu et al 2011). There have been conducted no similar European population-based surveys assessing the association between HMW adiponectin and MS, to the best of our knowledge. Associations between total adiponectin and various metabolic parameters in different population subgroups have been addressed in earlier Estonian studies (Jürimäe et al 2007, Jürimäe et al 2010), but the current study is the first one estimating serum HMW adiponectin level in a general population-based survey. As expected, we also found that MS was characterised by lower levels of serum HMW adiponectin and higher levels of insulin resistance as assessed by HOMA-IR. Accordingly, there was observed strong inverse correlation between insulin resistance and HMW adiponectin. It is well established that MS increases the risk of heart disease in both genders, although it seems to elicit a

greater impact in women (Ren et al 2009). Metabolic syndrome is a stronger predictor of cardiovascular disease in women than in men (Pischon et al 2008), and the effect of MS on left ventricular function and hypertrophy is greater in women than in men (Schillaci et al 2006). Considering the current findings about gender differences between HMW adiponectin and MS, we propose that hypoadiponectinaemia may be more strongly associated with metabolic syndrome in women than in men.

9.4. Association between HMW adiponectin levels and metabolic risk factors

We found HMW adiponectin to correlate positively with HDL cholesterol and negatively with obesity, insulin resistance, triglycerides and fasting glucose for both genders. For women only, we found HMW adiponectin to correlate negatively with 2-hour glucose in the OGTT, as well as with systolic and diastolic blood pressure. These results are similar to the outcomes of Andreasson *et al.* who observed gender-related differences in the association between adiponectin and cardiovascular risk factors: total adiponectin was associated with blood lipids both in men and women, but adiponectin was associated with glucose homeostasis more in women than in men (Andreasson et al 2012). Our study adds to this literature data by describing this relationship in terms of HMW adiponectin, instead of total adiponectin. In contrast, in a KORA survey, total adiponectin correlated to various metabolic risk factors in a pattern that was similar for both sexes (Rathmann et al 2007). We found HMW adiponectin to correlate to blood pressure exclusively in women. Clinical and experimental studies indicate causal relationship between low adiponectin and hypertension (Ohashi et al 2011), but it is still unclear to what extent this applies to men as well as to women. On the one hand, a recent Japanese study showed that serum HMW adiponectin concentrations were inversely associated with blood pressure in the general male population (Kawamoto et al 2011b). In contrast, earlier studies on Japanese (Tabara et al 2008), Chinese (Yu et al 2011) and on Thai subjects (Liu et al 2007) found no correlation between HMW adiponectin and systolic blood pressure. There exist significant differences in HMW adiponectin levels between different ethnic groups (Khan et al 2012), and to date most of relevant research has been carried out on Asian populations. Our study adds information about associations between HMW adiponectin and blood pressure specifically for Caucasians.

9.5. HMW adiponectin levels in metabolically healthy and unhealthy subjects

In metabolically healthy men, no correlations were found between HMW adiponectin and metabolic risk factors, with the exception of one risk factor: systolic blood pressure. Surprisingly, this relationship was not negative but positive. Our metabolically healthy group of men (n=52) had a mean systolic blood pressure of 119.8 ± SD 7.2 mmHg (range 88.0–129.0). On the contrary, a recent study from Japan found higher adiponectin to correlate with lower systolic and diastolic blood pressure in normotensive people (Baden et al 2013). Associations between HMW adiponectin and cardiovascular disease are complex and influenced by several conditions and factors (chronic heart disease, chronic kidney disease, cachexia, underlying disease state) (Okamoto et al 2011, Antoniades et al 2009). Therefore, this unexpected positive association between HMW adiponectin and systolic blood pressure in metabolically healthy men may be affected by other underlying factors. Unlike for metabolically healthy men, we found HMW adiponectin to correlate with HDL cholesterol, triglycerides and insulin resistance for the metabolically healthy female subgroup. Comparisons of metabolically healthy and unhealthy subjects showed, as expected, that metabolically unhealthy subjects were significantly older, had significantly higher BMI, waist circumference and HOMA-IR compared with metabolically healthy subjects in both genders. In addition, we found that for women only, metabolically healthy subjects had significantly higher HMW adiponectin levels compared with metabolically unhealthy subjects. This result is in line with our previous finding that HMW adiponectin correlates with metabolic risk factors for the group of metabolically healthy women but not for metabolically healthy men. To the best of our knowledge, previous studies have not described such gender differences in the relationship between HMW adiponectin levels and metabolic risk factors between metabolically healthy and unhealthy subjects. Whether and how this gender-specific difference influences the pathophysiologial processes through which HMW adiponectin influences health and disease is worthy of further study. It is known that testosterone reduces selectively the HMW form of adiponectin, which might contribute to the gender difference in adiponectin levels (Xu et al 2005). A recent study from Spain showed that adiponectin was related to free androgen index and sex hormone binding globulin levels in adolescents after adjusting for BMI and fat mass, suggesting an association between adiponectin and androgen bioavailability (Riestra et al 2013). On the other hand, serum adiponectin level was positively correlated with testosterone concentration in ageing (50–85 years) men but not in women (Yasui et al 2007). Thus, other factors besides testosterone might also play a role in the gender difference of adiponectin levels (Sun et al 2009).

9.6. Comparison of HMW adiponectin levels between metabolically healthy and unhealthy overweight/obese subjects

A subset of obese subjects seems to be protected from obesity-related cardiovascular and metabolic abnormalities. Metabolically normal obesity describes individuals with a body mass index of ≥ 30 kg/m^2 who do not have any overt cardiometabolic diseases such as type 2 diabetes mellitus, dyslipidaemia and hypertension. Components of metabolic syndrome, such as inflammatory markers and insulin sensitivity, have also been used to categorize subjects as metabolically healthy or unhealthy. However, it is not clear whether this metabolically healthy obese phenotype is just an early stage in the disease process that will ultimately progress to metabolically unhealthy obesity, or whether metabolically healthy obese people are relatively protected from developing the co-morbidities associated with obesity for the remainder of their lives (Pataky et al 2010). Within our overweight sample, the metabolically healthy subgroup was approximately 10 years younger than the metabolically unhealthy subgroup; it may still be that we are seeing two different snapshots of the same process in time, whereby metabolically healthy subjects tend to undergo transition to an increasingly metabolically unhealthy status over time. However, in contrast to this hypothesis, our obese sample showed similar age distributions for the metabolically healthy and unhealthy subjects. Hence our data does not allow us to refute either hypothesis. Future longitudinal studies could establish whether these metabolically healthy and unhealthy phenotypes are distinct only in time, or also by nature.

While there exist no established criteria for the definition of metabolically healthy obese individuals (Alam et al 2012), previous studies have reported that these individuals constitute approximately 6−35% of all obese subjects depending on the definition (Pataky et al 2010). A recent study from Finland showed that among obese subjects aged 45–74, the prevalence of the metabolically healthy obese phenotype, which was defined as the absence of metabolic syndrome, was 9.2% for men and 16.4% for women (Pajunen et al 2011). We defined the metabolically healthy status by strict criteria (subjects without impaired glucose regulation, dyslipidaemia, hypertension or insulin resistance) and found that 12% of obese subjects were metabolically healthy. Further analysis showed that in both genders, these metabolically healthy obese subjects had HMW adiponectin levels comparable to those of normal weight subjects. These results are in line with the outcomes of a recent study from Poland which did not find differences in HMW adiponectin concentrations between overweight or obese but metabolically healthy women, and normal weight controls, either (Bik et al 2010). Our data adds useful information to the notion that this phenomenon also exists in the case of obese but metabolically healthy Caucasian men. We found that among women with BMI ≥ 25 kg/m^2, HMW adiponectin levels were higher in metabolically healthy women compared with metabolically unhealthy women. We did not find a comparable difference for

men. However, among obese men, metabolically healthy men had significantly higher HMW adiponectin levels compared with metabolically unhealthy men. While we cannot explain this discrepancy, we are aware that the pathogenesis of metabolic disease is complex and includes various factors that are beyond the scope of this study. Kim *et al* have shown that mice that lacked leptine while overexpressing adiponectin had significantly higher levels of adipose tissue than their *ob/ob* littermates, but an improved metabolic profile (Kim et al 2007). Several other genetically modified murine models of obesity, with preserved insulin sensitivity, have been identified and common features of most of these models are an increased mass of non-visceral adipose tissue, a metabolically beneficial adipokine pattern, and a low amount of lipid deposition in the liver (Stefan et al 2013). Thus, there are many other adipocytokines, besides adiponectin, which modify the pathogenesis of metabolic disorders. Moreover, they are likely to influence each other's expression and production (Hajer et al 2008, Aprahamian et al 2011, Mattu et al 2013). We measured only one adipocytokine isoform (HMW adiponectin) and hence only focused on one aspect of the complex association between adipose tissue dysfunction and metabolic risk factors. Our study also had the following limitations**:** the possible complex effect of other underlying diseases (and medications used for other diseases) on HMW adiponectin levels could not be excluded; the metabolically healthy obese subgroup was very small; the definitions of the metabolically healthy obese phenotype have not been standardized; and BMI as a measure of obesity has limitations because it cannot distinguish between fat tissue and lean tissue. Despite these limitations, the study had also several strengths: the population-based approach; measuring not total but HMW adiponectin; strict criteria to define metabolically healthy subgroups; and impaired glucose regulation diagnosed by a comprehensive oral glucose tolerance test.

10. CONCLUSIONS

1. The prevalence of obesity in Estonian adult population was 32%. This indicator is significantly higher than previously estimated but comparable with recently reported data from other European countries.
2. Of the Estonian adult population 20% had impaired glucose regulation: the prevalence of IFG, IGT and diabetes was 5, 8 and 7%, respectively. This result is comparable to that reported from other European countries.
3. The prevalence of metabolic syndrome among the Estonian adult population was 26%, which is comparable to that in other European countries. However, in younger age men in Estonia had a significantly higher prevalence of metabolic syndrome compared with women (26% versus 13%, respectively).
4. The prevalence of insulin resistance was 5 times higher in subjects with metabolic syndrome but was not different between the premorbid and the morbid subgroups. This suggests that the concept of metabolic syndrome may be practically useful in early prediction of the life-time risk of cardiovascular disease and diabetes.
5. The HMW adiponectin level was significantly lower in all subjects with metabolic syndrome compared with those without metabolic syndrome.
6. Hypoadiponectinaemia is more strongly associated with metabolic syndrome in women than in men. Further studies are necessary to confirm these results in other populations and to elucidate whether adiponectin can influence the pathogenetic mechanisms of cardiometabolic diseases in a gender-specific manner in humans.
7. HMW adiponectin correlated positively with HDL cholesterol and negatively with obesity, insulin resistance, triglycerides and fasting glucose for both genders. For women only, we found HMW adiponectin to correlate negatively with 2-hour glucose in the OGTT, as well as with systolic and diastolic blood pressure.
8. For women only, metabolically healthy subjects had significantly higher HMW adiponectin levels compared with metabolically unhealthy subjects.
9. For metabolically healthy women, HMW adiponectin levels were associated with various metabolic risk factors but this association was not found for metabolically healthy men.
10. Twelve percent of obese subjects were metabolically healthy and this phenotype was characterized by HMW adiponectin levels similar to those observed in normal weight subjects of both genders.

11. SUMMARY IN ESTONIAN

Rasvumine, glükoosiregulatsiooni häired, metaboolne sündroom ja nende seosed kõrgmolekulaarkaaluga adiponektiini tasemega

11.1. Sissejuhatus

Viimase 30 aasta jooksul on rasvumise levimus maailmas kahekordistunud: 2008. aastal hinnati rasvumise levimuseks maailmas 10% meestel ja 14% naistel, kuid 1980. aastal vastavalt 5% ja 8% (Finucane jt 2011). Ülekaalulisuse ja rasvumise levimuse kiire tõus kogu maailmas viitab sellele, et põhjused on pigem seotud keskkonna, toitumise ja elustiili kui geneetiliste muutustega (Murphy jt 2013). Geneetiliste faktorite mõju tõttu on siiski ülekaalulisuse risk ja selle ulatus sarnases keskkonnas inimestel erinev (Haslam jt 2005, Walley jt 2009, Dixon 2010). Rasvumine on seotud paljude tervisehäiretega, nagu hüpertensioon, diabeet, düslipideemia, koronaarhaigus, südamepuudulikkus, maksahaigused, astma, sapikivitõbi, luu- ja liigeshaigused, depressioon ning pahaloomulised kasvajad (Clement jt 2010). Postiküsitluse tulemuste alusel hinnati 2008. aastal rasvumise levimuseks Eestis 16–64 aastaste isikute hulgas 18% (Tekkel jt 2008), kuid objektiivsetel mõõtmistel põhinevat populatsioonipõhist uuringut ei ole Eestis varem läbi viidud.

Metaboolne sündroom on riskifaktorite (rasvumine, glükoosiregulatsiooni häired, hüpertensioon ja düslipideemia) kogum, mille puhul esineb vähemalt viis korda kõrgem risk haigestuda 2. tüüpi diabeeti ja kaks korda kõrgem südameveresoonkonna haiguste risk (Eckel jt 2005, Mottillo jt 2010). Seoses rasvumise levimuse kasvuga suureneb ka metaboolse sündroomi levimus kogu maailmas (Cornier jt 2008). Üheksa Euroopa riigi andmete põhjal hinnati metaboolse sündroomi levimuseks meeste hulgas 32% ja naiste hulgas 29% (Qiao jt 2006). Eestis pole varem metaboolse sündroomi levimust uuritud. Kuigi metaboolse sündroomi patofüsioloogilised mehhanismid ei ole selged, peetakse võimalikuks keskseks mehhanismiks siiski abdominaalse rasvumisega kaasnevat insuliinresistentsust (Eckel jt 2005, Cornier jt 2008). Sellest tulenevalt on kõige olulisemaks metaboolse sündroomi kujunemist mõjutavaks riskifaktoriks rasvumine (Cameron jt 2009). Rasvumisel ja insuliinresistentsusel on oluline roll ka 2. tüüpi diabeedi kujunemisel (Murphy jt 2013). Seoses rasvumise leviku kasvuga tõuseb kogu maailmas ka glükoosiregulatsiooni häirete levimus (Shaw jt 2010). Eesti täiskasvanud elanikkonna kohta andmed diabeedi levimuse hindamiseks seni puudusid. Globaalsetes raportites hinnati ekstrapoleeritud Poola andmetele tuginedes diabeedi levimuseks Eestis 2000. aastal 4,4% (Wild jt 2004) ja 2010. aastal 9,9% (Shaw jt 2010). 2006. aastal läbiviidud väiksema populatsioonipõhise uuringu põhjal leiti, et diabeedi levimus Eesti ühes piirkonnas, Väike-Maarjas, oli 8,7% (Rajasalu jt 2008). Käesolev populatsioonipõhine uuring on esimene, mille tulemuste põhjal saab hinnata glükoosiregulatsiooni häirete reaalset levimust Eesti täiskasvanud rahvastikus. Viimases

Rahvusvahelise Diabeedi Föderatsiooni Diabeediatlases on käesolevat uuringut ka ühe allikana kasutatud ja diabeedi levimuseks Eesti täiskasvanud rahvastikus on märgitud 7,7% (International Diabetes Federation 2013).

Rasvkude on oluline endokriinorgan, mis toodab paljusid bioaktiivseid mediaatoreid ja hormoone (adipotsütokiine), mis mõjutavad hemostaasi, vererõhku, lipiidide ja glükoosi metabolismi ning ka põletiku ja ateroskleroosi kujunemist (Rabe jt 2008). Adiponektiin on rasvkoes toodetav hormoon, millel on insuliinitundlikkust parandavad, põletikuvastased, ateroskleroosivastased ja kardioprotektiivsed toimed ning vastupidiselt teistele rasvkoes toodetavatele hormoonidele on adiponektiini tase rasvumise ja sellega seotud seisundite puhul vähenenud (Scherer 2006). Adiponektiini sekreteeritakse madala ja kõrge molekulaarkaaluga isomeeridena, metaboolselt kõige aktiivsemaks peetakse just kõrgmolekulaarkaaluga (KMK) adiponektiini (Simpson jt 2010). KMK adiponektiini taseme osas on selge sooline erinevus: võrreldes meestega on naistel KMK adiponektiini tase oluliselt kõrgem (Xu jt 2005).

Enamasti on rasvumine seotud mitmete metaboolsete häirete kujunemisega, kuid siiski esineb rasvunute hulgas alagrupp, kellel metaboolseid häireid ei leita ja sellise fenotüübiga isikuid nimetatakse metaboolselt terveteks rasvunuteks (Pataky jt 2010). Võrreldes rasvunutega, kellel esineb metaboolseid häireid, on metaboolselt tervetel rasvunutel suurem nahaaluse ja väiksem vistseraalse rasva osakaal ning vähem ektoopilisi rasvaladestusi maksas ja skeletilihastes (Stefan jt 2013). Lisaks on leitud, et metaboolselt tervetel rasvunutel on võrreldes metaboolsete häiretega rasvunutega ka suurem insuliinitundlikkus, madalam põletikumarkerite tase, väiksem *intima-media* paksus ning kõrgem adiponektiini tase (Primeau jt 2011). Veelgi enam, on leitud, et metaboolselt tervete rasvunute adiponektiini tase on võrreldav normaakaaluliste isikute adiponektiini tasemega (Aguilar-Salinas jt 2008, Doumatey jt 2012). KMK adiponektiini taseme kohta metaboolselt tervetel rasvunutel on andmeid vähe – meie teada on ainult mõned uuringud, mille käigus on hinnatud KMK adiponektiini taset metaboolselt tervetel rasvunud naistel (Bik jt 2010, Elisha jt 2010).

11.2. Uuringu eesmärgid

1) Hinnata rasvumise, glükoosiregulatsiooni häirete ja metaboolse sündroomi levimust Eesti täiskasvanud elanikkonnas.
2) Analüüsida insuliinresistentsuse ja metaboolse sündroomi vaheliseid seoseid.
3) Kirjeldada soospetsiifilisi seoseid KMK adiponektiini taseme ja metaboolse sündroomi vahel.
4) Analüüsida metaboolsete riskifaktorite ja KMK adiponektiini taseme vaheliseid soospetsiifiliseid seoseid.
5) Võrrelda KMK adiponektiini taset metaboolsete häiretega ja häireteta uuritavatel.

11.3. Uuritavad ja meetodid

Rahvastikupõhine läbilõikeuuring viidi läbi kolmes Eesti maakonnas (Viljandi-, Põlva- ja Tartumaal) aastatel 2008–2009. Uuritavad valiti juhuslikult nelja perearsti nimistutest ning kutsuti uuringust osa võtma kirja teel (vastamismäär 53%). Lõpliku uuringugrupi moodustasid 495 uuritavat (214 meest, 281 naist) vanuses 20–74 aastat ja selle struktuur vastas 2009. aastal hinnatud Eesti rahvastiku vanuselisele ja soolisele struktuurile. Uuritavatel mõõdeti vererõhk, vööümbermõõt, pikkus ja kaal ning nad täitsid ankeedi haiguste ja riskifaktorite kohta. Kõikidel uuritavatel, kellel diabeeti varem diagnoositud ei olnud, tehti glükoositaluvuse proov ja kõikidel määrati paastuplasmast glükoosi, üldkolesterooli, HDL-kolesterooli, triglütseriidide, insuliini ja KMK adiponektiini väärtused. Rasvumist, ülekaalulisust ja glükoositaluvuse häireid diagnoositi Maailma Terviseorganisatsiooni (WHO) kriteeriumite alusel. Metaboolse sündroomi hindamiseks kasutati Rahvusvahelise Kolesterooli Õppeprogrammi Täiskasvanute III Ravipaneeli (NCEP ATP III) kriteeriume. Insuliinresistentsust defineeriti kui homeostaasi mudeli (HOMA) ülemist kvartiili kogu uuringugrupis (analüüsist jäeti välja varem diagnoositud diabeediga uuritavad). Metaboolse sündroomiga uuritavad jagati kahte alagruppi: esimese grupi moodustasid isikud, kellel ei olnud varem diabeeti, düslipideemiat ega hüpertensiooni diagnoositud, ja teise gruppi jäid uuritavad, kellel esines kasvõi üks eelpoolnimetatud häiretest. Kogu uuringugrupi lõikes jagati uuritavad metaboolselt terveteks (isikud, kellel ei esinenud glükoosiregulatsiooni häiret, düslipideemiat, hüpertensiooni ega insuliinresistentsust) ja metaboolsete häiretega grupiks (uuritavad, kellel esines vähemalt üks eelpoolnimetatud häiretest).

Statistilises analüüsis kasutati vabavaralist tarkvarapaketti R (versioon 2.15.3). Leiti rasvumise, glükoosiregulatsiooni häirete ja metaboolse sündroomi levimus ja 2009. aastal hinnatud Eesti rahvastiku struktuurile kaalutud levimus (%) koos 95% usalduspiiridega. Levimuse võrdlemiseks kolme vanusegrupi vahel kasutati hii-ruut testi koos Bonferroni korrektsiooniga. Pidevate tunnuste esitamiseks arvutati mediaanid ja kvartiilidevahed või keskväärtused ja standardhälbed. Mann-Whitney U testiga võrreldi erinevaid alagruppe. Spearmani osalist korrelatsioonikordajat kasutati kõrgmolekulaarkaaluga adiponektiini ja metaboolsete rikifaktorite vaheliste seoste hindamiseks. Mitmest logistilist regressioonianalüüsi kasutati metaboolse sündroomi riskifaktorite hindamiseks. ROC-kõverate abil võrreldi kõrgmolekulaarkaaluga adiponektiini ja insuliinresistentsuse homeostaasi mudeli ennustavat väärtust metaboolse sündroomi hindamisel. Lubatud statistilise vea piiriks valiti 5% ($p<0.05$). Uuringul on Tartu Ülikooli Eetikakomitee luba.

11.4. Tulemused

Rasvumise, glükoosiregulatsiooni häirete ja metaboolse sündroomi levimus
Rasvumise kaalutud levimus oli 32%. Meeste ja naiste vahel statistiliselt olulist erinevust ei esinenud. Diabeedi kaalutud levimus oli 7%, olulist soolist erinevust ei leitud. Diabeedi levimus suurenes vanuse kasvades ning peaaegu pooled (49%) diabeedijuhtudest olid varem diagnoosimata. Paastuglükoosi häire ja glükoositaluvuse häire kaalutud levimused olid vastavalt 5% ning 8%. Glükoosiregulatsiooni häire esines 20%-l uuritavatest.

Metaboolse sündroomi kaalutud levimus oli 26% ja suurenes oluliselt vanusega. Ainuke sooline erinevus metaboolse sündroomi levimuse osas oli noorimas vanusegrupis: meestel esines metaboolset sündroomi võrreldes naistega oluliselt rohkem (vastavalt 26% *versus* 13%).

Seosed metaboolse sündoomi ja insuliinresistentsuse vahel.
Metaboolse sündroomi alagruppide võrdlus
Metaboolse sündroomiga isikutest olid insuliinresistentsed 62% ja ilma metaboolse sündroomita 12% uuritavatest. Metaboolse sündroomiga uuritavad, kellel varem düslipideemiat, diabeeti ega hüpertensiooni diagnoositud ei olnud, olid oluliselt nooremad, madalama süstoolse vererõhu, väiksema kehamassiindeksi ja vööümbermõõduga kui need, kellel oli varasemalt diagnoositud kasvõi üks nimetatud häiretest. Metaboolse sündroomi alagrupid ei erinenud lipiidide väärtuste ega insuliinresistentsuse poolest.

KMK adiponektiini soo- ja vanusespetsiifilised erinevused
Meestega võrreldes oli naistel KMK adiponektiini tase oluliselt kõrgem. Antud sooline erinevus jäi kehtima ka peale kohandamist vööümbermõõdu, kehamassiindeksi ning diabeedi-, vererõhu- ja lipiide langetavate ravimite suhtes. KMK adiponektiini ja vanuse vahel oli statistiliselt oluline positiivne seos.

KMK adiponektiini seosed metaboolse sündroomi ja insuliinresistentsusega
Metaboolse sündroomiga isikute hulgas oli KMK adiponektiini tase nii naistel kui meestel oluliselt madalam, võrreldes uuritavatega, kellel metaboolset sündroomi ei esinenud. Peale kohandamist vanuse, kehamassiindeksi ja insuliinresistentsuse suhtes jäi pöördvõrdeline seos KMK adiponektiini ja metaboolse sündroomi vahel oluliseks ainult naistel. ROC-kõverate analüüs näitas, et homeostaasi insuliinresistentsuse mudel prognoosis nii meestel kui naistel metaboolse sündroomi esinemist täpsemini kui KMK adiponektiin. Peale kohandamist vanuse ja kehamassiindeksi suhtes jäi meestel endiselt homeostaasi insuliinresistentsuse mudel paremaks, kuid naistel erinevust ei olnud.

KMK adiponektiini seosed metaboolsete riskifaktoritega
Seoseid hinnati kohandatuna vanusele. Nii meestel kui naistel oli KMK adiponektiin positiivselt seotud HDL-kolesterooliga ning negatiivselt triglütseriidide, vööümbermõõdu, kehamassiindeksi, homeostaasi insuliinresistentsuse mudeli, paastuinsuliini ja paastuglükoosiga. Naistel esines lisaks veel negatiivne seos kõrgmolekulaarkaaluga adiponektiini ja süstoolse ning diastoolse vererõhu ja glükoositaluvuse proovis 2 tunni veresuhkru väärtuse vahel.

KMK adiponektiini tase metaboolsete häiretega ja häireteta isikutel
33% uuritavatest (27% meestest ja 37% naistest) ei esinenud metaboolseid häireid. Antihüpertensiivseid ravimeid tarvitas 27%, statiine 4% ja diabeedi-ravimeid 4% uuritavatest ning ravimite tarvitamise osas soolist erinevust ei olnud. Suitsetamisel ja alkoholitarbimisel olulist seost KMK adiponektiini tasemega ei leitud. Meeste hulgas esinesid seosed metaboolsete riskifaktorite ja KMK adiponektiini vahel ainult metaboolsete häiretega isikute alagrupis, kuid naistel lisaks ka metaboolsete häireteta alagrupis. Metaboolsete häireteta naistel oli KMK adiponektiini tase oluliselt kõrgem kui metaboolsete häiretega naistel. Meestel sarnast erinevust ei leitud. Nii meeste kui naiste puhul olid metaboolsete häireteta isikud, võrreldes metaboolsete häiretega isikutega, oluliselt nooremad, väiksema vööümbermõõdu ja madalama kehamassiindeksiga.

KMK adiponektiini tase metaboolsete häiretega ja häireteta ülekaalulistel ja rasvunud uuritavatel
Nii meeste kui naiste hulgas olid kehamassiindeksiga ≥ 25 kg/m^2 metaboolsete häireteta uuritavad oluliselt nooremad ja väiksema vööümbermõõduga kui metaboolsete häiretega uuritavad. Insuliinresistentsuse osas olid metaboolsete häireteta uuritavad võrreldavad normaalkaaluliste isikutega. KMK adiponektiin oli kehamassiindeksiga ≥ 25 kg/m^2 metaboolselt tervetel naistel, võrreldes metaboolsete häiretega naistega, oluliselt kõrgem ja samas võrreldav normaalkaaluliste naistega. Metaboolselt tervete rasvunute osakaal kõigist rasvunutest oli 12%, mis ei erinenud meeste ega naiste osas. Metaboolselt tervete rasvunute KMK adiponektiini tase oli võrreldav normaalkaaluliste uuritavate omaga nii meestel kui naistel. Metaboolselt terved rasvunud olid võrreldes metaboolsete häiretega rasvunutega oluliselt vähem insuliinresistentsed. Keskmise vanuses osas metaboolselt terved ja metaboolsete häiretega rasvunud aga ei erinenud.

11.5. Järeldused

1) Rasvumise levimus Eesti täiskasvanud elanikkonnas oli 32%. See on oluliselt kõrgem kui varasemalt hinnatud, kuid võrreldav hiljuti avaldatud andmetega teistest Euroopa riikidest.
2) 20% Eesti täiskasvanud elanikkonnast esines glükoosiregulatsiooni häire: 5% paastuglükoosi häire, 8% glükoositaluvuse häire ja 7% diabeet. See tulemus on võrreldav teistes Euroopa riikides saadud tulemustega.
3) Metaboolse sündroomi levimus Eesti täiskasvanud rahvastikus oli 26%, mis on sarnane teiste Euroopa riikide vastavate näitajatega. Nooremate meeste seas oli metaboolse sündroomi levimus nooremate naistega võrreldes oluliselt kõrgem (vastavalt 26% *versus* 13%).
4) Metaboolse sündroomiga uuritavate hulgas oli insuliinresistentsuse levimus viis korda kõrgem kui isikutel, kellel metaboolset sündroomi ei esinenud. Metaboolse sündroomiga uuritavate alagrupp, kus varasemalt hüpertensiooni, diabeeti ega düslipideemiat diagnoositud ei olnud, ei erinenud insuliinresistentsuse poolest alagrupist, kus nimetatud häired olid juba varasemalt diagnoositud. Seetõttu aitab metaboolse sündroomi diagnoosimine kardiovaskulaarhaiguse ja diabeedi riski hinnata võimalikult vara.
5) KMK adiponektiini tase oli metaboolse sündroomiga uuritavate hulgas oluliselt madalam kui isikutel, kellel metaboolset sündroomi ei esinenud.
6) Hüpoadiponektineemia ja metaboolse sündroomi vaheline seos oli naistel meestega võrreldes tugevam. Vajalikud on edasised uuringud, et seda tulemust ka teistes rahvastikurühmades kinnitada ja selgitada, kas adiponektiin võib mõjutada kardiometaboolsete haiguste patogeneetilisi mehhanisme soospetsiifiliselt.
7) Nii naistel kui meestel oli KMK adiponektiini ja HDL-kolesterooli vahel positiivne ning KMK adiponektiini ja rasvumise, insuliinresistentsuse, triglütseriidide ja paastuglükoosi vahel negatiivne seos. Ainult naistel esines lisaks ka negatiivne seos KMK adiponektiini ja 2 tunni glükoosi väärtusega glükoositaluvuse proovil ning süstoolse ja diastoolse vererõhuga.
8) Ainult naiste hulgas oli metaboolsetelt tervetel uuritavatel KMK adiponektiini tase metaboolsete häiretega isikutega võrreldes oluliselt kõrgem.
9) KMK adiponektiini tase oli seotud mitmete metaboolsete riskifaktoritega ainult metaboolselt tervete naiste hulgas.
10) 12% rasvunutest olid metaboolselt terved ja nende KMK adiponektiini tase oli sarnane normaalkaaluliste isikute KMK adiponektiini tasemega nii meestel kui naistel.

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