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Tiina Maarit Ahonen

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A Gender-Specific View

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ABSTRACT:

The metabolic syndrome (MetS), a cluster of risk factors for cardiovascular disease and type 2 diabetes, is associated with low-grade inflammation, a state in which several cytokines are secreted from adipose tissue. Decreased adiponectin and increased interleukin-1 receptor antagonist (IL-1Ra) levels have been observed with the MetS. Elevated levels of C-reactive protein (CRP), a general inflammatory marker, often appear with metabolic diseases. There is existing evidence of gender differences in relation to the MetS as a cardiovascular risk or inflammatory markers associated with metabolic diseases. The role of low-grade inflammation in the development of these diseases is not well-known.

This study was aimed at obtaining gender-specific information about the association of adiponectin and low-grade inflammation, measured by high sensitivity- CRP (hs-CRP) and IL-1Ra, with the factors that often precede the MetS (e.g. weight gain, elevated blood pressure and smoking), and with the course of the MetS. The study population consisted of five age groups of inhabitants in the town of Pieksämäki (n=1294), who were invited for a health check-up in 1997-1998 and again in 2003-2004. Of the invited subjects, 923 (71.3%, 411 men and 512 women) participated in the first check-up and 681 subjects of them in the second check-up.

The results indicate that decreased adiponectin and increased hs-CRPand IL-1Ra levels were associated with a relative change in body mass index from the age of 20 years to middle age in women, but not in men. The proportion of women with lower socio-economical status increased with relative weight gain; in men there was no association. Decreased adiponectin levels in females and increased hs-CRP levels in males were associated with smoking. Women with elevated blood pressure and the MetS had significantly higher levels of hs-CRP and IL-1Ra compared to men. The risk for the MetS was threefold in hypertensive women with the lowest tertile of adiponectin; no association was seen in men. Decreased baseline adiponectin and increased baseline IL-1Ra levels were associated with both the appearance and the persistence of the MetS; increased baseline hs-CRP levels were linked with the persistence of the MetS.

In conclusion, from the aspect of low-grade inflammation, greater relative weight gain is more harmful to women than to men. Women, who smoke may be more prone to development of inflammatory state due to decreased adiponectin levels compared to men. Decreased adiponectin level and increased low-grade inflammation may refer to an unfavorable course of the MetS in both genders.

National Library of Medicine Classification: WG 340, WK 820, WD 200
Medical Subject Headings: Metabolic Syndrome X; Adiponectin; Smoking; C-Reactive Protein; Hypertension; Interleukin 1 Receptor Antagonist Protein; Sex Factors; Body mass index

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TIIVISTELMÄ:

Metabolinen oireyhtymä, sydän- ja verisuonisairauksien ja diabeteksen riskitekijöiden keräytymä, on yhteydessä matala-asteiseen tulehdukseen. Metabolisissa sairauksissa on havaittu alentuneita adiponektiinin ja kohonneita interleukiini-1 reseptori antagonistin (IL-1Ra) ja C-reaktiivisen proteiinin (CRP) pitoisuuksia. Tulehduksen merkkiaineiden pitoisuuksissa sekä metaboliseen oireyhtymään liittyvässä sydän- ja verisuonisairauksien riskissä on havaittu sukupuolten välisiä eroja. Matala-asteisen tulehduksen merkitys metabolisten sairauksien kehittymisessä tunnetaan vaillinaisesti.

Tämän tutkimuksen tarkoituksena oli lisätä tietoa matala-asteisen tulehduksen yhteydestä metabolista oireyhtymää usein edeltäviin tekijöihin – painon nousuun, kohonneeseen verenpaineeseen ja tupakointiin – sekä tutkia mahdollisia sukupuolten välisiä eroja. Tutkimusväestö muodostui Pieksämäen kaupungin viidestä ikäluokasta, jotka kutsuttiin terveystarkastukseen vuosina 1997–1998 ja uudelleen 2003–2004.

Tutkimuksessa havaittiin, että naisilla suhteellisen painoindeksin (BMI) nousu 20 vuoden iästä keski-ikään oli yhteydessä merkitsevästi alentuneeseen adiponektiinipitoisuuteen ja lisääntyneeseen herkän CRP:n (hs-CRP) ja IL-1Ra:n pitoisuuteen. Alempaan sosiaaliluokkaan kuuluvien naisten osuus lisääntyi merkitsevästi painon nousun myötä. Miehillä tulehduksen merkkiaineilla tai sosiaaliluokalla ja BMI:n muutoksella ei ollut yhteyttä. Naisilla havaittiin yhteys tupakoinnin ja matalan adiponektiinipitoisuuden välillä. Miehillä oli todettavissa yhteys kohonneen hs-CRP:n ja tupakoinnin välillä. Naisilla, joilla oli kohonnut verenpaine ja metabolinen oireyhtymä, oli merkitsevästi suuremmat hs-CRP – ja IL-1Ra-pitoisuudet kuin vastaavilla miehillä. Naisilla adiponektiinipitoisuuden alimpaan kolmannekseen liittyi kolminkertainen riski saada metabolinen oireyhtymä. Miehillä tätä yhteyttä ei ollut. Tässä tutkimuksessa lähtötason alentunut adiponektiinipitoisuus ja suurentunut IL-1Ra -pitoisuus liittyivät metabolisen oireyhtymän ilmaantumiseen ja pysyvyyteen.

Johtopäätöksenä voidaan todeta, että matala-asteisen tulehduksen näkökulmasta suurempi suhteellinen painonnousu on haitallisempaa naisille kuin miehille. Tupakoivilla naisilla havaittu matalampi adiponektiinitaso tupakoiviin miehiin verrattuna voi viitata tupakoivien naisten olevan alttiimpia matala-asteisen tulehduksen kehittymiselle. Matala adiponektiinipitoisuus ja suurentunut tulehdusmerkkiaineiden taso ennakoi tämän tutkimuksen mukaan epäsuotuisaa metabolisen oireyhtymän kulkua molemmilla sukupuolilla.

Yleinen suomalainen asiasanasto: metabolinen oireyhtymä; adiponektiini; c-reaktiivinen proteiini; interleukiinit; painoindeksi; sukupuolierot; tupakointi; verenpainetauti

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Laukaa October 31st, 2012 Tiina Ahonen

List of the original publications

This dissertation is based on the following original publications:

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II Ahonen TM, Kautiainen HJ, Keinänen-Kiukaanniemi SM, Kumpusalo EA, Vanhala MJ. Gender difference among smoking, adiponectin and high-sensitivity C-reactive protein. *American Journal of Preventive Medicine.2008; 35:598-601.*

III Ahonen T, Saltevo J, Laakso M, Kautiainen H, Kumpusalo E, Vanhala M. Gender differences relating to metabolic syndrome and proinflammation in Finnish subjects with elevated blood pressure. *Mediators of Inflammation.2009; 959281:1-6.*

IV Ahonen TM, Saltevo JT, Kautiainen HJ, Kumpusalo EA, Vanhala MJ. The association of adiponectin and low-grade inflammation with the course of metabolic syndrome. *Nutrition, Metabolism and Cardiovascular Disease. 2012; 22:285-91.*

Contents

Abbreviations

AACE	American Association of Clinical Endocrinologists
ACE	Angiotensin-converting enzymes
ADA	American Diabetes Association
AHA	American Heart Association
ANCOVA	Analysis of covariance
ATP III	Adult Treatment Panel III
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
EGIR	European Group for the Study of Insulin Resistance
ER	Endoplasmic reticulum
FFA	Free fatty acids
HDL	High density lipoprotein
HOMA	Homeostasis model assessment
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
IL-1Ra	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
LDL	Low-density lipoprotein
MetS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung and Blood Institute
OGTT	Oral glucose tolerance test
OR	Odds Ratio
QUICKI	Quantitative insulin sensitivity check index
SD	Standard deviation
T2D	Type 2 diabetes
TNF	Tumor necrosis factor
TZD	Thiazolidinedione
VLDL	Very low-density lipoprotein
WHO	World Health Organization
WHR	Waist-to-hip ratio

1 Introduction

The metabolic syndrome (MetS) is a cluster of classical risk factors like hypertension, dyslipidemia, glucose intolerance and obesity, which are associated with cardiovascular diseases (CVD) and type 2 diabetes (T2D) (1, 2, 3). There is still no conclusive idea of the pathophysiology of the MetS (3). There are also multiple definitions of the MetS. This has caused confusion and the question of the clinical usefulness of this syndrome has been raised; does the MetS identify subjects at risk for CVD or T2D better than traditional risk scores? Though no consensus exists, there is significant evidence showing that traditional risk factors tend to be aggregated in an individual and, moreover, subjects with the MetS have increased risk for CVD and T2D (4, 5, 6).

Obesity and the MetS are nowadays known to be associated with low-grade inflammation (7). In this condition, a variety of cytokines are secreted mainly from adipose tissue, which is thus considered as an important endocrine organ (8). Decreased levels of anti-inflammatory adiponectin have been detected in connection with coronary artery disease, central obesity and the MetS (8-13). There is also evidence suggesting that adiponectin has a role in regulation of the inflammatory network (14). Elevated levels of interleukin-1β (IL-1β), one of the major pro-inflammatory cytokines, and interleukin-1 receptor antagonist (IL-1Ra) have been detected in obesity and features of the MetS (15-20). In addition, the well-known marker of inflammatory conditions, C-reactive protein (CRP), is elevated in CVD, obesity and the MetS; furthermore, levels of CRP seem to be regulated by inflammatory cytokines and centrally located adiposity (21-25). Smoking, the traditional risk factor for CVD, is also associated with central fat accumulation and increased levels of inflammatory markers (26, 27).

Aside from obesity itself, fat distribution seems to play a role in the development of metabolic disorders. In particular, visceral fat deposits contribute to insulin resistance and are associated with CVD risk and the MetS (28, 29, 30). There have been observed gender differences in the risk of CVD and T2D in relation to fat distribution, the levels of inflammatory markers and the MetS (31-34). Additionally, diabetic women seem to be at higher risk of CVD events, compared to diabetic men (35, 36). Also, IL-1β and IL-1Ra secretions are regulated differently between genders (37).

With the increase in obesity and the number of diabetic subjects there exists a great challenge to identify early enough those individuals with an increased risk for CVD and T2D. The MetS may help in estimating this risk. However, a better understanding of the pathophysiology of the MetS would increase the usefulness of this risk cluster in clinical practice.

Due to the growing evidence of the involvement of low-grade inflammation in the pathophysiology of the metabolic disorders, this population-based study was aimed at obtaining new, gender-specific information about the association of adiponectin and low-grade inflammation with factors that often precede the MetS – like weight gain, elevated blood pressure and smoking – and getting information about the markers of low-grade inflammation related to the course of the MetS.

2 Review of the literature

2.1 METABOLIC SYNDROME

2.1.1 Brief history with different definitions of the metabolic syndrome

Hypertension, hyperglycemia and gout are often found in the same people. This was first noticed by the Swedish physician Kylin in 1923. His finding is commonly considered as the first description of the metabolic syndrome (MetS) (38). More than 20 years later, Vague published research results showing upper-body (android or male-type) adiposity associated with the metabolic disturbances repeatedly seen with cardiovascular disease (CVD) and type 2 diabetes (T2D) (39). Subsequently, associations between obesity and lipids and glucose metabolism, and their possible connections with CVD have been under investigation (40, 41). These disturbances were not, however, considered as a cluster of risk factors until Reaven in 1988 described "Syndrome X", a combination of hypertension, abnormal glucose metabolism, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol and hyperinsulinemia, which increases the risk of CVD and T2D (42). According to Reaven, insulin resistance with compensatory hyperinsulinemia was the central part of this syndrome, but he did not include obesity itself to be an etiological factor. Afterwards this cluster came to be called by other names, such as "The Insulin Resistance Syndrome" (43) or "The Deadly Quartet" (44). In the first attempt of a worldwide definition for this constellation of risk factors, the term "metabolic syndrome" was recommended, and although there has been competition between this term and others, "metabolic syndrome" is nowadays preferred and has gradually become established.

In 1998, the World Health Organization (WHO) published the first worldwide definition for the MetS (45). This definition was based on insulin resistance (defined by hyperinsulinemia, impaired glucose tolerance (IGT) or T2D as a basic component). At least two of the additional factors (obesity, hypertriglyceridemia, low HDL cholesterol levels, hypertension and microalbuminuria) were needed to fulfill the MetS criteria in this definition (Table 1). The primary purpose of the WHO definition was to identify those individuals with the MetS who were at high risk of developing CVD or, among non-diabetics, developing T2D. In practice, this definition proved difficult to use. The oral glucose tolerance test (OGTT) could be required, and among subjects with normal glucose tolerance, insulin resistance was proven with the expensive and time-consuming glycemic clamp technique. Additionally, the WHO definition was criticized because of the inclusion of microalbuminuria in the criteria, while there was no consensus about the association of microalbuminuria with insulin resistance (46, 47).

The European Group for the Study of Insulin Resistance (EGIR) published the following year a modified criteria for the MetS with the purpose of establishing a more suitable tool for practice (48). Insulin resistance was also the essential component in this definition, but it was defined by fasting insulin. Two or more of the additional factors (obesity, dyslipidemia, hypertension and elevated fasting glucose) were required for the diagnosis of the MetS. Meanwhile, microalbuminuria was removed from the criteria. Central obesity

was determined for the first time in this definition with sex-specific limits of waist circumference instead of waist-to-hip ratio (WHR), which was used in the earlier definition. Furthermore, different cut-off points were used in dyslipidemia compared to the WHO definition. In the EGIR definition, diabetic subjects were excluded. (Table 1)

A new approach to determining the MetS was undertaken in 2001 by the National Cholesterol Education Program (NCEP) Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, ATP III) with a definition that equally treated each component (waist circumference, hypertriglyceridemia, low HDL cholesterol levels, blood pressure and glucose) (1). The MetS was defined by the existence of three or more of the abovementioned factors, which made this definition simple to use in clinical practice. Another notable difference, compared to the two earlier definitions, was the lack of insulin resistance determination in this definition. (Table 1)

Two years later, the American Association of Clinical Endocrinologists (AACE) returned to the first two definitions of the MetS by introducing a new definition which included insulin resistance as its central focus (49). It also recommended the use of the term "Insulin resistance syndrome". This definition had IGT, dyslipidemia with reduced HDL cholesterol or elevated triglycerides, elevated blood pressure and obesity as its major criteria; other factors which could affect the MetS diagnosis were a family history of CVD or other atherosclerotic diseases, or T2D, polycystic ovary syndrome and hyperuricemia. Diabetic subjects were excluded from this definition. (Table 1)

Multiple different definitions of the MetS caused confusion both in practice and in research work. Additionally, it proved necessary to take ethnicity into account (e.g. the increased risk for T2D or CVD appeared in Asians with lower body mass index (BMI) and waist circumference, compared to Europeans) (50 - 53). In 2005, the International Diabetes Federation (IDF) published new criteria for the MetS in which central obesity was a compulsory basic element (54). Central obesity was evaluated by waist circumference with ethnic- and gender-specific cut-off points. Otherwise, at least two additional factors (such as fasting glucose, HDL cholesterol, fasting triglycerides and hypertension) were needed for the MetS diagnosis. The cut-off points in these parameters were similar to the ATP III definition, except for lower fasting glucose, which was adopted according to the new criteria of impaired fasting glucose recommended by the American Diabetes Association (ADA) in 2003, in which hyperglycemia is determined by fasting glucose ≥ 5.6 mmol/l (55).

The same cut-off point of glucose was included in the later updated NCEP/ATP III criteria, which otherwise stayed unchanged, compared to the original criteria. There was seen to be no reason to make other changes in this updated ATP III criteria; by this argument, the definition placed no emphasis on a single underlying factor of the MetS (4).

The task of unifying the diagnostic criteria of the MetS is ongoing. The representatives of IDF and the National Heart, Lung and Blood Institute (NHLBI) / American Heart Association (AHA) have tried to solve the remaining disagreements, giving a statement in 2009 on the new clinical diagnostic criteria of this syndrome (56). They agreed that waist circumference should not be a prerequisite for diagnosis, but instead one of five criteria; the diagnosis is made on the basis of three criteria being present.(Table 1) Furthermore, it was acknowledged that waist circumference needs long-term prospective studies to be determined with adequate ethnic- and gender-specific limits.

Table 1. Definitions of the metabolic syndrome (1, 4, 45, 48, 49, 54, 56)

	WHO (1998)	EGIR (1999)	NCEP (2001)	AACE (2003)	IDF (2005)	Updated NCEP (2005)	AHA/NHLBI (2009)
Required factors	F-Ins in top 25%; F-Gluc ≥6.1 mmol/l; 2-hGluc≥7.8 mmol/l	F-Ins in top 25%	Not specified	High risk of being insulin resistant	Waist: ethnic -specific	Not specified	Not specified
	AND ≥2 OF:	AND ≥2 OF:	≥3 OF:	AND ≥2 OF:	AND ≥2 OF:	≥3 OF:	≥3 OF:
F-Gluc (mmol/l)		≥ 6.1	≥ 6.1	≥ 6.1	≥5.6	≥5.6	≥ 5.6
HDL (mmol/l)	<0.9 (m) <1.0 (w)	<1.0	<1.03 (m) <1.29 (w)	<1.03 (m) <1.29 (w)	<1.03 (m) <1.29 (w)	<1.03 (m) <1.29 (w)	<1.0 (m) <1.3 (w)
	or	or					
Triglycerides (mmol/l)	≥1.7	>2.0	≥1.7	≥1.7	≥1.7	≥1.7	≥1.7
	or drug tr.	or drug tr.	or drug tr.	or drug tr.	or drug tr.	or drug tr.	or drug tr.
Obesity	WHR>0.9 (m) >0.85 (w) BMI≥30 kg/m²	W:≥94 cm (m) ≥80 cm (w)	W:≥102 cm(m) ≥88 cm (w)		W:≥94 cm (m) ≥80 cm (w) (in Europeans)	W:≥102 cm (m) ≥88 cm (w)	W: population and country-specific
BP mmHG	≥140/90 or drug tr.	≥140/90 or drug tr.	≥130/85 or drug tr.	≥130/85 or drug tr.	≥130/85 or drug tr.	≥130/85 or drug tr.	≥130/85 or drug tr.
Microalb.uria	U-albumin≥20µg/min						

F-Ins= fasting insulin, F-Gluc=fasting glucose, HDL=high-density lipoprotein, (m) = men, (w)= women, drug tr. = drug treatment, WHR= waist-to-hip ratio, W=waist, BMI= body mass index, BP = blood pressure

2.1.2 Prevalence of the metabolic syndrome

Estimation of the prevalence of the MetS is dependent on the definition used, as well as on the age, gender and ethnic make-up of the population. Among 8608 U.S. adults included in the Third National Health and Nutrition Examination Survey (NHANES) cohort in 1988-1994, the age-adjusted prevalence of the MetS was 23.9% (using the NECP definition) and 25.1% (according to the WHO definition) (57). When the revised NCEP definition was used for 6436 subjects from the NHANES III, the age-adjusted prevalence was 29.2%; for the 1677 subjects in the NHANES 1999-2000 cohort, the age-adjusted prevalence was 32.3% (58). For the 3601 subjects in the NHANES 1999-2002 cohort, the unadjusted prevalence was 34.5% on the basis of the NCEP definition and 39.0%, according to the IDF definition (59). When the WHO, NCEP and IDF criteria were compared in relation to middle-aged adults from the San Antonio Heart Study, the NCEP criteria showed increased prevalence compared to the WHO, but lower prevalence compared to the IDF criteria (60).

Outside the USA, the prevalence of the MetS has also been reported to vary with the definition used. In an Australian population-based survey of more than 11,000 subjects (AusDiab), the prevalence of the MetS according to NCEP, WHO, IDF and EGIR definitions was 22.1%, 21.7%, 30.7% and 13.4%, respectively (61). Among a population of African origin, prevalence of the MetS was also estimated to be higher with the IDF definition, compared to the NCEP and the WHO definitions (30.3%, 28.1%, 24.8%, respectively) (62). In an Indian epidemiological study (CURES-34), the MetS prevalence estimates were 25.8% using the IDF, 18.3% using the NCEP and 23.2% using the WHO definitions (63). Though prevalence of the MetS often seems to be higher with the IDF definition, the opposite also appears, with lower prevalence when using the IDF criteria compared to the NCEP definition (64, 65).

Inconsistent definition-related differences in the prevalence of the MetS may be due to ethnic-specific waist circumference included in the IDF definition. Additionally these prevalence rates depend on whether diabetic subjects are or are not included in the study population.

In terms of the prevalence estimates of the MetS, there is some variation between genders. In the NHANES III, the age-adjusted prevalence rates in men were slightly higher compared to women (31.4% vs. 27.0%, respectively) whereas in the NHANES 1999-2000 cohort the prevalence of the MetS showed a trend of being greater in women than in men (32.9% vs. 31.8%) (58). Although, prevalence estimates in many studies usually only vary by some percentages between genders, there are other studies with a wide range between gender-specific prevalence rates of the MetS: in males in a representative Australian population, prevalence rates were noticeably higher compared to women (24.4% vs. 19.9.% with ATP: III and 34.4% vs. 27.2% with IDF criteria); in a Greek population of 2282 subjects, the prevalence rates were 25.2% in men and 14.6% in women (ATP:III criteria); and in the FINRISK cohort of 2049 middle-aged subjects, the prevalence of the MetS was 38.8% in men and 22.2% in women, according to the WHO definition (61, 66, 67). On the other hand, there is also evidence of greater prevalence rates among women compared to men:

in a Chinese population of 15540 subjects (17.8% vs. 9.8% with ATP: III), in the study of 10368 subjects in Iran (40. 5% vs. 24% with ATP: III, 41.0% vs. 21.0% with IDF), and in a Spanish study (28.8% vs. 22%, n=2540, with ATP: III) (68, 69, 70). Accordingly, the prevalence estimates of the MetS between genders vary inconsistently. According to the literature to date, the reason for this gender-specific difference between the MetS prevalence rates is actively under investigation. It has been speculated that it is related to various factors like hormonal, socio-economical, occupational and more widely cultural aspects (71-77). Naturally gender-specific variations in MetS prevalence may be partly explained by the racial or ethnic composition of studied populations (57).

The prevalence of the MetS is clearly age-dependent. In the NHANES III cohort, the prevalence rates between three age groups (20-39 years, 40-59 years and ≥ 60 years) of males were 10.2%, 29.3% and 42.6%, respectively. In females, the corresponding rates were 9.7%, 26.0% and 43.9%, respectively (58). Age-related increases in MetS prevalence have been observed worldwide (63, 65, 66). However, a decrease or a plateau after the sixth or the seventh decade of life occurs in the prevalence of the MetS in some studies (66, 78). This may be explained by higher mortality, caused especially by metabolic disorders or obesity-related diseases in these age groups.

With increasing obesity in younger age groups, features of the MetS are also found in children and adolescents (79). Diagnosis of the MetS in these age groups is difficult because of the lack of consensus of what criteria or definition to use (80, 81). This also entails difficulties when estimating prevalence of the MetS in children or adolescents (82). On the other hand, there is strong evidence that metabolic disorders present in childhood are important predictive factors for cardiovascular risks in adulthood (83, 84).

In Finland, one of the first studies to determine the prevalence on the MetS was conducted in 1993-94, before any international definition of this syndrome was assessed. The MetS was defined as a clustering of dyslipidemia (hypertriglyceridemia, low HDL cholesterol, or both) and insulin resistance (abnormal glucose tolerance, hyperinsulinemia, or both), with the result that the MetS was present in 17% of men and in 8% of women (85). The MetS was also found to be more common in men in another Finnish study, where NCEP and IDF definitions of the MetS were compared in a non-diabetic population in the years 1992 and 2002. According to NCEP criteria, the MetS was present in 45.4% of men in 1992 and in 46.9% of men in 2002. In women, the corresponding rates were 28.4% and 35.5%, respectively. When the IDF criteria were used, 48.7% of men vs. 34.5% of women had MetS in 1992 and 49.7% of men vs. 42.2% of women in 2002. The notable thing in these rates is the fact that although the prevalence of the MetS increased in both genders over this period of ten years, the increase was statistically significant only in women: $p=0.002$ (according to NCEP) and $p=0.001$ (according to IDF criteria) (86). The researchers found the increase in prevalence could be explained by increasing abdominal obesity and abnormalities in glucose metabolism. With increasing obesity, it can be assumed that MetS prevalence rates will increase worldwide in the future.

2.1.3 Characteristics of the metabolic syndrome

Classical components of the MetS are insulin resistance, presented as a central part of this syndrome by Reaven (42) and hypertension, glucose intolerance, dyslipidemia and also

(abdominal) obesity (44). Several other conditions (like the prothrombotic state, the pro-inflammatory state, endothelial dysfunction, hyperuricemia, polycystic ovary syndrome and obstructive sleep apnea) are associated with the MetS (4, 87). The prothrombotic state and the pro-inflammatory state were even considered as major components of this syndrome in the report of the NHLBI/AHA conference in 2004 (88). Genetics, hormonal factors, lifestyle aspects (like physical activity, smoking and diet), socio-economical factors and aging also have an effect on the development of features of the MetS.

An alternative way of classifying the components of the MetS is to divide them by metabolic risk factors and underlying risk factors. The metabolic risk factors are well-known risks for atherosclerotic cardiovascular diseases like dyslipidemia, elevated plasma glucose and hypertension, while insulin resistance, abdominal obesity, and associated conditions (e.g. physical inactivity, aging and hormonal alterations, the pro-inflammatory state) are considered as underlying risk factors (4).

Thus, the concept of the MetS is multidimensional. As seen in different definitions of the MetS, there are varying opinions of which components of the MetS are the most central ones and which factors play secondary roles. The fact that the MetS appears individually with different components present in one person (4) shows further challenges, both to research and clinical work concerning the MetS.

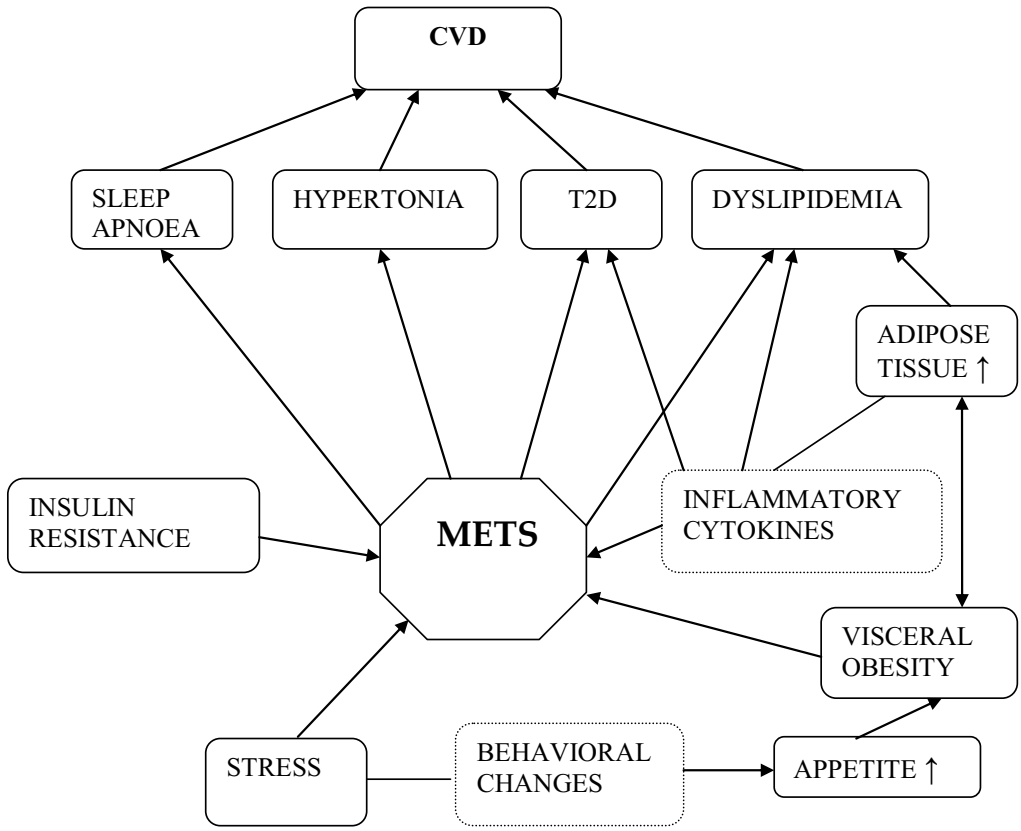


Figure 1. Conditions involved with the development of the metabolic syndrome (METS)

2.2 PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME

Competing theories have made multiple attempts to explain the pathophysiology of the MetS. On the other hand, it is generally acknowledged that for a syndrome with this many features there is no possibility of finding a single or common cause, but instead there are several factors which affect the development of the MetS (4). In the AHA/NHLBI conference report, these factors have been grouped into three categories: obesity and associated adipose tissue-derived factors, insulin resistance, and independent factors that mediate components of the MetS. In every category, there are both genetic and acquired underlying causes. Additionally in this report, contributing factors such as aging, pro-inflammation and multiple endocrine factors are mentioned (88). On the other side, there are researchers who consider insulin resistance to be the only factor capable of uniting the components of the MetS, and thus consider it to be the main pathogenic cause (87, 89). With obesity increasing worldwide and, furthermore, the present knowledge of how adipose tissue acts as an active endocrine organ and can secrete a variety of anti- and pro-inflammatory cytokines, the present conception of the pathophysiology of the MetS includes visceral obesity and low-grade inflammation in particular as remarkable factors (7, 14, 90, 91, 92). Hypoadiponectinemia has also been considered as a link between insulin resistance and obesity (93). (Figure 1)

2.2.1 Insulin resistance

Insulin, the hormone secreted by β-cells in the islets of Langerhans, has multiple effects on carbohydrate, lipid and protein metabolism. Insulin acts as the main regulator of blood glucose levels: insulin concentration is elevated with the rise of blood glucose levels and stimulates glucose uptake in muscle cells and adipocytes. It also inhibits hepatic glucose production by inhibiting gluconeogenesis in the liver. Insulin regulates lipid metabolism by both stimulating lipogenesis and inhibiting lipolysis. A condition of impaired insulin action in its main target tissues, liver, skeletal muscle and adipocytes is referred to as insulin resistance, though insulin resistance is often determined in a more glucocentric way, with impaired insulin action resulting in hyperinsulinemia to maintain euglycemia (87, 90, 91).

Insulin resistance has been identified and measured with multiple markers. The euglycemic hyperinsulinemic clamp is considered as a golden standard, although it is time consuming and expensive. For that reason e.g. fasting insulin and OGTT as well as computational models, the homeostatic model assessment (HOMA) and the quantitative insulin check index (QUICKI) have been used both in clinical and in research work to determine insulin resistance (6, 94). Both of the models mentioned have proven to be useful tools both in research and clinical work and even comparable to the euglycemic hyperinsulinemic clamp, especially in obese subjects (94).

During the fasting state, the skeletal muscle energy supply comes mainly from fat oxidation and it is changed into glucose oxidation with the rise of blood glucose levels (95). Elevated blood glucose levels stimulate insulin secretion, which in turn suppresses lipolysis and increases glucose uptake into muscle cells. Glucose uptake is the main function of insulin as muscle tissue is concerned; and skeletal muscle because of its large

quantity plays a valuable role in maintaining glucose homeostasis (91, 96). As much as 90% of the glucose uptake occurs in skeletal muscle (97).

The fact that insulin resistance is associated with obesity has been well-known for decades. It has since been demonstrated that insulin resistance appears with weight gain even when weight still remains within normal limits, and also when obese subjects still have normal glucose tolerance (98, 99). Muscle insulin resistance is associated with an accumulation of fat in muscle tissue, especially in intramyocellar spaces (100). There is an overabundance of free fatty acids (FFA) in blood circulation because triglycerides stored in adipose tissue are free to mobilize in the absence of the antilipolytic effects of insulin (101). Triglycerides have been hypothesized to independently interfere with insulin action in muscle, but on the other hand there is also evidence that they would act as a surrogate marker for some other fatty-derived factor, most likely long-chain acyl-CoA species, which have been found to exist in muscle cells in a strong negative correlation with insulin sensitivity (102, 103). Long-chain acyl-CoA is involved in the destruction of the insulin-signaling cascade, which normally begins with the insulin binding to its receptor (102). Increased intramyocellar fat and fatty acid metabolites are possibly the main factors in the development of insulin resistance in skeletal muscle. This theory is supported by the finding that in subjects with high BMI but low intramyocellar lipids, there is observed normal insulin sensitivity; controversially, in a lean subject with low BMI but high intramyocellar lipids, decreased insulin sensitivity appears (102). The cause for this unfavorable development is still inadequately known and may also involve genetic, inherited and inflammatory defects, in addition to obviously acquired cause, like obesity (104, 105).

An excess of FFAs also contributes to the development of insulin resistance in the liver by enhancing hepatic glucose output and the production of triglycerides, as well as an increased secretion of very low-density lipoproteins (87, 90). Additional impairments in lipid metabolism include a decrease in HDL cholesterol and an increased density of LDL (87). Increased hepatic glucose production leads to an increased secretion of insulin, which however is not capable of suppressing glucose secretion; thus there is insulin resistance in the liver. Paradoxically, in this insulin resistance state, regarding lipid metabolism, the insulin action in the liver is strengthened with insulin contributing to the liver's ability to produce more triglycerides (102).

Insulin resistance of adipose tissue is firmly associated with the MetS (88, 89, 90, 102). Overabundance of FFAs reduces glucose uptake in adipocytes and, in the state of insulin resistance, lipolysis is accelerated with diminished insulin action, leading to a further increased release of FFAs (106). Centrally and viscerally located adipose tissue contributes especially to increased FFA flux and insulin resistance (107, 108, 109). Visceral adipocytes have been observed to be more sensitive to lipolysis than adipocytes in subcutis (110). According to portal theory, this excessive visceral lipolysis causes the liver to turn insulin resistant with direct drainage of FFAs to portal circulation. This theory has recently been convinced in an animal model (111). Additionally, adipose tissue seems to induce insulin resistance with the pro-inflammatory cytokines it secretes (112).

Insulin receptors are commonly expressed in several tissues. Insulin action is described as an insulin signaling pathway which begins with insulin binding to its receptor. This

binding exerts a chain of phosphorylation-dephosphorylation reactions, which affect glucose transportation, glycogen synthesis and glycolysis, for example (104). In muscle cells, insulin binding to its receptors leads to tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1) protein, which in turn activates phosphatidylinositol 3-kinase (PI3K). This activation enhances glucose transport and also affects the activation of nitric oxide (NO) production (113). Another route in insulin signaling is a mitogenactivated protein kinase (MAPK) pathway, in which there are mediated growth hormone properties of insulin, and which is involved in inflammation, cell proliferation and atherogenesis (113, 114). In the insulin resistance state, the insulin signaling pathway is severely disturbed in the PI3K route but functions normally in the MAPK pathway (114). The latter pathway is over-stimulated by compensatory hyperinsulinemia and worsens the insulin resistance state (113).

A defect of the endoplasmic reticulum (ER), the vast membranous network organelle responsible for protein metabolism, is also involved in insulin resistance (115). In ER stress, the situation which is created when newly synthesized unfold proteins accumulate in the ER in overabundance; a mechanism of unfolded protein response is activated. This mechanism is associated with inflammatory signaling systems, like the activation of inflammatory kinases, which results in an inhibition of insulin action. Reactive oxygen species (ROS), products of organelle stress, also impair insulin action and increase production of inflammatory cytokines (115). Thus ER stress leads to metabolic dysfunction.

Insulin sensitivity and resistance is not a two-step condition, but instead a continuous process. When study subjects were divided into four groups according to fasting glucose levels (low-normal fasting glucose, high-normal fasting glucose, impaired fasting glucose (IFG), and combined impaired fasting glucose and impaired glucose tolerance (IGT)), it was found that insulin sensitivity is inversely related to glycemia, even within the normal fasting glucose range (116). Similarly, in a large study of 6414 Finnish men, insulin sensitivity was impaired already at relatively low glucose levels within the normal range of fasting glucose and 2-hour glucose levels (117). Additionally, a difference between IFG and IGT groups was found: compared to normal glucose tolerance, in isolated IFG both basal and total insulin releases were reduced, while in isolated IGT they were increased. This finding shows decreased insulin secretion to be a major defect in isolated IFG, while in isolated IGT the fault lies in peripheral insulin resistance (117). In earlier results concerning the site of insulin resistance, it was postulated that in IFG there is marked insulin resistance of the liver and milder resistance in peripheral tissues, but in IGT insulin resistance is just the opposite (118). These combined results suggest that at least partially different metabolic characteristics underlie IFG and IGT. In the glucose intolerance state, impaired insulin sensitivity is compensated with hyperinsulinemia, which is maintained with an increase in pancreatic β-cell mass, insulin synthesis and/or secretion (119). When this compensation fails, defects of insulin secretion become dominant because of glucolipotoxicity, the condition in which pancreatic β-cells are damaged due to excess concentrations of glucose and lipids, even though physiological levels of glucose and lipids are essential for normal β-cell function (6, 119).

Insulin resistance is an independent predictor of not only of T2D, but also hypertension and CVD (120). Though a natural consequence of obesity, insulin resistance does not affect all obese people; conversely, among obese subjects those with insulin resistance have a higher risk of CVD, compared to those without insulin resistance (120). Among newly diagnosed T2D subjects, there frequently appear signs of CVD (121). Subjects with T2D but without former myocardial infarction are known to share a similar risk of myocardial infarction, compared to subjects with former infarction but lacking T2D (122). Insulin resistance is speculated to act as a common link between obesity, CVD and T2D, possibly via low-grade inflammation (120, 123).

2.2.2 Obesity

During the last decades, an excess of body adiposity has become an epidemic, especially in Western countries. In the USA, the prevalence of being overweight (BMI ≥ 25 kg/m²) was 72.3% among men and 64.1% among women, and the corresponding prevalence rates for obesity (BMI≥30 kg/m²) were 32.2% and 35.5%, respectively, according to NHANES 2007-2008 data (124). Obesity prevalence in the U.S. has more than doubled in 25 years (from 15% of obesity prevalence in 1980) (125). Excess weight gain is a global epidemic (126). In 2008, according to the WHO estimation, there were 1.5 billion overweight adults in the world, of whom over 200 million men and nearly 300 million women were obese (127). In the National Finriski 2007 survey, among Finnish people aged 25-74 years, 66% of men and 52% of women were overweight (BMI≥ 25 kg/m²) and percentages of obesity (BMI≥30 kg/m²) were 19% and 21%, respectively (128).

Causes of weight gain are natural consequences of the westernized life style, with its excess of energy together with a sedentary lifestyle. These changes are a part of wide socio-economical alterations which have during the last ten to twenty years also affected developing countries where occupational structures have moved from agricultural work to industrial and service fields, motorized transport has developed, and household income has increased (126, 129). The underlying mechanisms of being overweight and obesity are only partially understood. They are complex and even controversial (129). Alterations of lifestyle probably explain obesity worldwide, but the cause of individual obesity is also involved with genetic factors (130). Obesity-associated diseases and metabolic disturbances are thus presumed to result from and be modified by gene-environment interaction (131).

A person's amount of body fat can be assessed with accurate methods, like measuring total body water or total body potassium, using bioelectrical impedance or dual-energy x-ray absorptiometry. In particular, the degree of abdominal obesity is most accurately determined by using MRI or CT technology (132). However, these methods are expensive and hardly available in research work or clinical practice. Instead, a more practical approach for determining body fat and degree of obesity is to measure BMI, waist circumference or WHR; all are widely used in clinical work and in epidemiological research (132, 133). There is disagreement about the usefulness of these methods in risk assessment in relation to obesity-associated diseases, especially when there is increasing evidence about central and particularly visceral obesity associated with the risk of T2D and CVD (134, 135). However, there is a lot of documentation that by these simple

measurements it is possible to assess both body fat and its association with metabolic diseases in clinical practice (132, 136, 137).

2.2.2.1 Fat distribution

Since the first descriptions of the MetS, especially upper body adiposity has been found to be associated with this syndrome. Vague determined fat distribution with the brachio-femoral fat ratio and named lower ratios as gynoid adiposity and higher ratios as android (male) type adiposity, firmly associated with metabolic consequences (39). In later research, fat distribution was divided into abdominal fat type, commonly seen in males, and peripheral fat type, in which fat is located in the gluteal-femoral region, as typically seen in women. Furthermore, with increasing volume fat seems to be stored equally in subcutaneous and visceral compartments in men, whilst in women increasing fat mass is first stored mainly in subcutaneous areas (138). Overweight men have been observed to have, even after body fat matching, a stronger risk profile for CVD than women; however, this difference seems to disappear among overweight women who have male-type abdominally distributed fat deposits (31). With CT scanning, it has been possible to further separate and divide centrally located fat into visceral and subcutaneous fat (139). In particular, visceral fat deposits contribute to insulin resistance and are associated with CVD risk and the MetS (28, 29, 30).

All people with excess fat mass do not develop metabolically detrimental features (metabolically healthy obese subjects). Controversially, people have been identified with normal BMI but increased risk for the MetS, CVD and T2D (metabolically obese normal weight subjects) (140, 141). In obese people with metabolic disease, there has found to be more visceral fat compared to metabolically healthy obese individuals. Likewise, metabolically obese normal weight subjects usually have more visceral fat compared to subjects with similar weight but no metabolic disease (140, 141). Earlier results also show visceral fat depots, which account for less than 20% of total body fat at the most, to be metabolically the most active (142). Subcutaneous adipocytes are more sensitive to insulin's antilipolytic effects and less sensitive to catecholamine-induced lipolysis than visceral adipocytes (143). Factors determining fat location are not thoroughly elucidated, but include the influence of sex hormones, glucocorticoids, genetic and also environmental factors (8, 144,145).The proportion of visceral fat increases with age and in women with menopause (146,147). Though subcutaneous adipose tissue may not have as detrimental a role as visceral fat in the development of the MetS, and has even been considered beneficial in context of the MetS, excessive subcutaneous fat also needs to be considered as pathogenic (8, 148).

Additionally, there is evidence that both a lack and an excess of adipose tissue can emphasize metabolic disturbances. In lipodystrophy syndromes, states with decreased amounts of both subcutaneous and visceral fat, there is a strong association between insulin resistance, hyperglycemia, dyslipidemia and fatty liver (149). Without sufficient adipose tissue, FFAs are not stored adequately and may thus accumulate in muscle and the liver, which causes insulin resistance in these organs and may also lead to lipotoxicity (150). On the other hand, with an excess of body fat there may also appear a deficiency in fat storage in adipose tissue (149). The hypothesis of adipose tissue expandability is

presumed to answer this controversial situation: the metabolic consequences of an individual are dependent on, instead of the total amount of adipose tissue, the capability of adipose tissue to expand to store lipids (148). At the point where adipose tissue expansion is no longer possible, metabolic disturbances appear with fat accumulation in non-adipose tissue like liver, muscle and pancreatic β-cells. In these ectopic sites, lipids are thought to cause insulin resistance in a lipid-induced toxic way, thus sharing the same kind of mechanism of lipotoxicity, regardless of amount of adipose tissue (148, 150). There is support to this theory in an animal model with ob/ob mice, in which a vast increase in degree of obesity did not impair insulin sensitivity nor cause fat accumulation in the liver, but instead an increase in subcutaneous adipose tissue was associated with remarkable metabolic improvement in these mice (151). In humans as well, this theory receives support with evidence that larger subcutaneous adipocytes are associated with the development of T2D and, more recently, from studies which show that thiazolidinedione insulin sensitizers (TZD), in spite of weight gain, improve insulin sensitivity and reduce fat accumulation in the liver (152,153). Thus adipocytes are, with enlargement, thought to lose their efficiency as metabolic buffers. This phenomenon lets non-adipose tissues be exposed to excessive fluxes of lipid fuels, leading to insulin resistance in extra-adipose tissues, like liver and skeletal muscle. TZDs are speculated to stimulate adipocyte differentiation and to create new smaller adipocytes with lipid-buffering capability, thus diminishing insulin resistance (154).

The location of visceral fat in the abdominal cavity enhances the flux of FFAs to the liver (portal theory), but more recent research has proven visceral and peripheral adipose tissue to be distinct also in genetic issues (155). On the other hand, genetic research results are also contradictory (156). Further research of the reasons and effects of fat distribution regarding the MetS is lively and ongoing and definitely needed to construct a coherent overview.

2.2.3 Low-grade inflammation in the development of the metabolic syndrome

With increasing knowledge of adipose tissue as an endocrine and immune organ, rather than just a store of energy, there have appeared new aspects regarding the role of this tissue in the development of the MetS. In addition to adipocytes, which form approximately 50% of the cellular content of adipose tissue, this tissue consists of macrophages, endothelial cells, pre-adipocytes, nerve tissue, connective tissue matrix, leucocytes and fibroblasts (8, 14, 157). Adipose tissue secretes several cytokines which have anti- or pro-inflammatory effects (8). Cytokines produced mainly, though not solely, by adipose tissue are called adipocytokines. These proteins act as soluble mediators and regulators in multiple endocrine functions. Noticeably, not all cytokines (even though they may partly be produced by adipocytes) are called adipocytokines; however, there are contradictions in terminology regarding this issue (7, 14, 92).

Adipose tissue excess, particularly viscerally located, is firmly associated with the pro-inflammatory state (88). There is a large body of research evidence proving that adipose tissue depots differ in the degree of metabolic properties with enhanced activity in visceral adipose tissue compared to subcutaneous adipose tissue (142,158). Additional evidence suggests that subcutaneous adipose tissue in the abdominal region probably differs from

peripheral subcutaneous adipose tissue with higher metabolic activity (e.g. increased production of inflammatory cytokines), though it does not reach as high activity as visceral adipose depot (159). Along with cytokines, synthesis of other inflammatory markers, like C-reactive protein (CRP), is increased in obesity and insulin resistance (14).

There appears to be growing evidence concerning the association between the MetS and low-grade inflammation (160, 161). This association is supported by both decreased levels of anti-inflammatory cytokines and increased levels of pro-inflammatory cytokines present with the MetS (161, 162, 163). The adipocytokines adiponectin and leptin, chemokines tumor necrosis factor-α (TNF-α) and IL-6 are most frequently associated with insulin resistance (14).

2.2.3.1 Adiponectin

Adiponectin was first described approximately 15 years ago. This protein is secreted mainly by adipose tissue, but it is also produced by myocytes, both in skeletal and in cardiac muscles; it is also present in bone marrow (164, 165). Adiponectin is expressed more in subcutaneous, than in visceral adipose tissue compartment (8). It has been named with several terms like adipocyte complement-related protein of 30 kilodalton (Acrp30), AdipoQ and gelatin-binding protein of 28-kilodalton (GBP28). The term adiponectin, however, is an established one (8, 166). Two adiponectin receptors have been identified: AdipoR1, which is widely expressed in muscle, and AdipoR2, which is present mainly in the liver (8, 167).

Adiponectin concentrations in human plasma are between 5 to 30 μg/ml in lean subjects, and concentrations are higher in women than in men (166). On the contrary, compared to other adipocytokines, adiponectin concentrations are lower in obese subjects than in non-obese subjects; furthermore, concentrations are inversely associated with the amount of visceral adipose tissue (166, 168). Additionally, plasma adiponectin levels decrease with insulin resistance, T2D and ischemic heart disease (166,168,169,170). Decreased adiponectin concentrations are also associated with elevated plasma triglyceride and decreased plasma HDL-cholesterol levels (11, 171). In hypertension, there exist low adiponectin levels as well (10, 172). Thus, the classical components of the MetS are involved with hypoadiponectinemia, which has even been suggested as a potential additional component of the MetS by some researchers (12, 13). Adiponectin concentration also decreases with an increase in the number of components of the MetS (12).

Adiponectin may act as a promoter in the network of pro- and anti-inflammatory cytokines; with decreased synthesis of adiponectin, the control mechanisms of the production of many pro- and anti-inflammatory cytokines are probably inhibited (14). Adiponectin is capable of suppressing the reactions caused by TNF, which has even been considered as its main anti-inflammatory function, and it enhances the production of anti-inflammatory cytokines like interleukin-10 and interleukin-1 receptor antagonist (IL-1Ra) (14).

In studies of Pima Indians, in whom there is expressed a high prevalence of obesity and T2D, individuals with higher adiponectin levels had a lower risk of diabetes in longitudinal studies (173). Furthermore, neither low waist circumference nor low fasting glucose was as protective as higher adiponectin levels as regards the risk of T2D (173).

Independently of traditional risk factors, higher adiponectin levels were also associated with lower myocardial infarction risk in men in a prospective follow-up study of six years (174). Later research has observed positive associations between lower adiponectin concentrations and obesity-related malignancies (like breast, prostate, endometrial and colon cancers) (175). Thus, multiple studies refer to the protective role of adiponectin in several diseases, but the functional mechanisms behind it are not totally understood.

Adiponectin circulates in blood in three main forms: trimer, hexamer and high-molecular weight form, with the latter putatively being the most insulin-sensitizing (92). Adiponectin increases fatty acid oxidation and glucose uptake in muscle and reduces gluconeogenesis in the liver; these effects are partly mediated through activation of AMP-activated protein kinase (AMPK) (176). Furthermore, research results with mice showed that adiponectin elevates plasma insulin levels when injected intravenously (177). Adiponectin concentration is inversely associated with weight gain. In obesity, adiponectin receptors are also down-regulated; however, these changes are restored with weight loss (178). Additionally, adiponectin concentrations have been found to rise with exercise and also with dietary intake of linoleic or omega-3 fatty acids (179, 180). With smoking there emerges a decrease in adiponectin levels, even dose-dependently (181). Intake of certain drugs like fenofibrates, statins, angiotensin-converting enzymes (ACE) inhibitors and TZDs are associated with elevated adiponectin concentration (182, 183). The physiological mechanisms behind the changes of adiponectin concentration are not elucidated and the research results concerning these issues are ambiguous. The challenge is to find out the mechanism of adiponectin decrease with weight gain. This finding would probably lead to a better understanding of the whole cytokine network.

2.2.3.2 Interleukin 1-β and Interleukin 1-receptor antagonist

Interleukin-1 (IL-1) was first described with studies concerning the endogenous mediators of fever (184). IL-1, which is referred to as a prototypic pro-inflammatory cytokine, consists of two distinct ligands, interleukin 1-alpha (IL-1α) and interleukin 1-beta (IL-1β), both of which are synthesized as large precursor proteins (185). Though first isolated from leukocytes, interleukins are secreted from several non-leukocytic cells and also from adipose tissue (8, 17, 184). There exist two primary receptors for IL-1α and IL-1β, with a type I receptor being responsible for most IL-1 mediated actions (185). Within the IL-1 family, there also appears a natural antagonist for IL-1α and IL-1β, the IL-1 receptor antagonist (IL-1Ra). This anti-inflammatory member of the IL-1 group is produced by the same cells as IL-1α and IL-1β and competitively binds to the IL-1 type I receptor, thus preventing IL-1 signaling (185). Later research has revealed other members of the IL-1 family, and this expansion has led to new nomenclature. Also IL-1β and IL-1Ra have new systemic names (IL-1F2 and IL-1F3, respectively), but the names first mentioned are still widely used in research (186).

Elevated levels of IL-1β and IL-1Ra have been detected in subjects with essential hypertension and with atherosclerosis (15, 16, 17, 187). In the development of type 1 diabetes, IL-1β has been demonstrated to mediate impairment of the function of pancreatic β-cells (188). IL-1β even inducts apoptosis in human Langerhans islets (189). Furthermore, a high concentration of glucose has been shown to induce the production and secretion of

IL-1β in human pancreatic β-cells. According to this finding, there have been suggestions that IL-1β might be involved in the pathogenesis of T2D as well (190). IL-1Ra, as expected of an IL-1 antagonist, seems to protect pancreatic β-cells from glucose-induced impairment and apoptosis (190). On the other hand, there is controversy in the research, with some results showing that high glucose does not induce IL-1β production in pancreatic islets and the mechanism of β-cell death is different in type 1 diabetes, compared to β-cell death in T2D (191). Decreased levels of IL-1Ra have been reported with T2D patients, whereas elevated IL-1Ra levels have been detected in insulin resistance and obesity and precede the onset of T2D (18, 192, 193, 194). In the pre-diabetic state, an increase in IL-1Ra levels has been shown to be the most sensitive marker for cytokine response (19). Also with the MetS, the levels of IL-1Ra seem to correlate positively (18, 195).

Levels of IL-1β are usually not elevated in the circulation of healthy individuals in contrast to IL-1Ra, which is constantly present (16,185). In unstable coronary arterial disease, there appears an elevated level of IL-1β but no corresponding elevation of IL-1Ra levels, which points to inflammatory dominance (196). A low IL-1Ra/IL-1β ratio is present with newly diagnosed insulin dependent diabetes mellitus. This ratio, however, seems to return to normal values with the chronic diabetes (197). On the other hand, in knee osteoarthritis the IL-1Ra/IL-1β ratio was found to be highly elevated (198). As far back as two decades ago, it was demonstrated that a 10- to 100-fold excess of IL-1Ra over IL-1β suffices to block the effects of IL-1β on pancreatic islets (199). There is growing evidence that pro- and inflammatory cytokines function in a tight connection. For example, adiponectin is known to be capable of inducing the production of IL-1Ra and suppressing several inflammatory cytokines (14, 167). However, the mechanisms behind the activation of the innate immune system, which affects the levels of pro- and anti-inflammatory cytokines or their reciprocal balance, are not fully understood, not even between IL-1β and its natural antagonist IL-1Ra.

2.2.3.3 C-reactive protein

C-reactive protein (CRP) is a first described acute phase reactant and an indicator of systemic inflammation or inflammatory condition, e.g. tissue damage by cancer or trauma (200). CRP concentration is determined by genetic factors, but in particular centrally located adiposity is considered to be a major determinant of CRP levels (25). Synthesis of CRP is occurring in hepatocytes and it is stimulated by IL-1 and IL-6 (23). There is also some evidence that CRP would be synthesized in some other cells, like in macrophages within atherosclerotic lesions; these results, however, have been contradicted by later studies (201, 202). However, when adipocytes isolated from human adipose tissue were incubated with inflammatory cytokines IL-1β and IL-6, CRP production was seen in these adipocytes (203). CRP concentrations in healthy subjects are from around 1 mg/l to less than 10 mg/l, but in acute phase response the concentration can rapidly increase to the level of 400 mg/l (204). With high-sensitivity CRP (hs-CRP), one is referred to newer immunoassay methods with a sufficient sensitivity to measure CRP through the normal range (and even below 1 mg/l), instead of less sensitive standard assays; hs-CRP is not a novel protein.

Three decades ago, it was demonstrated that CRP binds specifically to LDL and VLDL (205). Elevated CRP levels have been detected to correlate positively with BMI, with insulin resistance measured by HOMA, and negatively with HDL levels (206). Among hypertensive subjects, CRP concentrations are often elevated (21). With increasing knowledge of inflammation as an important factor in cardiovascular diseases that is also associated with the MetS, the question has arisen of a possible role of CRP in the atherosclerotic process (207, 208, 209). Among initially healthy middle-aged men, a strong relationship was demonstrated between CRP levels and the future risk of a coronary event, even with low levels of CRP (210). Among middle -aged women as well, the level of CRP was found to be the most powerful predictor of the risk of a future cardiovascular event, even in women with low cholesterol levels (211). On the other hand, among a large Reykjavik Study population, even though CRP levels were found to be stable from decade to decade and thus a usable risk predictor, they were only a relatively moderate predictor of future cardiovascular risk. Furthermore, CRP levels (compared to established traditional risk factors) could not add predictive value, except very marginally (212).

In the study concerning associations between CRP and the features of the MetS, there was found to be a positive correlation between CRP and diabetes, uric acid and BMI, with the strongest correlation between CRP and BMI (213). Additionally, CRP levels were found to increase with the number of the components of the MetS (213). According to some researchers, CRP has even been suggested as an optional component of the MetS (14,214,215). CRP levels of >3mg/L were found to add prognostic information at all levels of severity of the MetS in the assessment of future cardiovascular risk (216). This cut-off point is in line with the recommendation of the Centers of Disease Control and Prevention /AHA Statement, in which the risk for cardiovascular disease has been classified according to CRP-levels as follows: low risk = CRP<1mg/L; average risk = 1.0mg/L<CRP<3.0mg/L; and high risk = CRP>3 mg/L (217). In a Japanese study, the cut-off point of hs-CRP for the MetS was recommended to be 0.65 mg/l (218).

It is still unclear whether CRP is just a marker or an active participant of an inflammatory process. There is, however, evidence, that measurement of CRP may be useful in early prediction of future diabetes and cardiovascular risk, also among subjects with the MetS (215). Furthermore, hs-CRP is capable of providing further information about the MetS because of its strong connection with those MetS components which are difficult to measure, like fibrinolysis and insulin resistance (214, 219). These arguments, taken together with the fact that traditional risk factors are lacking in every fifth case of coronary heart disease, reflects the need for other risk factors. CRP is a potential candidate to fulfill this demand, especially with its currently inexpensive cost (220).

2.2.3.4 Other inflammatory markers associating with the metabolic syndrome

TNF-α is considered as a first pro-inflammatory link between obesity and insulin resistance (221). It is produced mainly by macrophages and lymphocytes, but only in lesser concentrations from human adipocyte, which has led to the idea that elevated TNF-α levels seen in obesity are probably not regulated by adipose tissue (92). However, TNF-α levels are positively associated with fasting insulin, waist circumference, and triglycerides and negatively with HDL-levels. Furthermore, TNF-α concentration increases in parallel

to the number of the MetS components (222).The synthesis of TNF-α is suppressed by adiponectin (14).

Leptin, a pro-inflammatory cytokine produced mainly by adipocytes, is known to control appetite. It is secreted mainly by subcutaneous adipose tissue and its concentration correlates positively with the percentage of body fat (223). Initially leptin was thought to decrease food intake and weight gain in brain level, but there have been later observations according to which decreased leptin levels after weight loss signal the hypothalamus to reduce energy expenditures and to increase feeding to regain weight (224). These observations have led to the hypothesis that by inhibiting declines in leptin levels during weight gain, it would be possible to maintain weight loss (224). This hypothesis is supported by results in mice where leptin increased the effect of sibutramin by increasing fatty acid oxidation and decreasing food intake (225). Leptin levels have been found to predict the development of the MetS, independently of obesity (226).

IL-6 is secreted from adipose tissue, with higher levels from visceral than subcutaneous compartments (221). IL-6 is known to induce the hepatic production of CRP and is thus related to elevated CV risk. Moreover, due to direct drainage from visceral adipose tissue to the portal vein, it has been speculated that IL-6 levels contribute to hepatic metabolism by enhancing VLDL secretion and hypertriglyceridemia (227). Elevated IL-6 levels are also strongly associated with decreased insulin sensitivity (227).

In addition to the abovementioned cytokines, there are several other ones (like resistin, visfatin and plasminogen activator inhibitor-1, together with the more recently discovered vaspin and omentin), all of which contribute to the development of insulin resistance (14, 92). The network of these cytokines, which are mainly secreted by adipose tissue, is complex. Although actively being researched, they are still insufficiently understood. That said, they are charged with expectations as a potential link in the missing connections between obesity, inflammation and the MetS.

2.3 HYPERTENSION, LOW-GRADE INFLAMMATION AND THE METABOLIC SYNDROME

Elevated blood pressure is associated with insulin resistance or hyperinsulinemia (228,229). Intravenously administered insulin reduces urinary sodium excretion when given to subjects of normal weight (230). Insulin resistance is associated with increased sodium reabsorption, but also with impaired vasodilatation, which could be one potential reason for the development of hypertension in the insulin resistant state (231, 232).

Low-grade inflammation has been presumed to be an independent risk factor for hypertension (233). In essential hypertension, there appear decreased adiponectin concentrations as well as elevated levels of IL-1β and IL-1Ra, IL-6 and TNF-α, for example. Furthermore, CRP levels are increased (9, 15, 16, 17, 233). Hypoadiponectinemia has been speculated to have a role in the pathogenesis of hypertension, probably via insulin resistance but also through activation of the inflammatory network and endothelial dysfunction (234). Moreover, a decrease in adiponectin levels may increase vascular smooth muscle proliferation, leading to arterial stiffness (234). The idea that low-grade inflammation impairs endothelial function is supported by findings that by causing

inflammation with Salmonella typhi vaccination, IL-6 levels are elevated and, moreover, there emerges a strong resistance to vasodilating stimuli in vessels (235). Thus a possible mechanism between low-grade inflammation and hypertension could be due to an imbalance between vasodilating and vasoconstricting factors; low-grade inflammation may have an effect on the synthesis and degradation of these substrates, with nitric oxide being one possible target (233). In hypertensive (but not in normotensive) rats, there has been shown a direct vasoconstriction caused by IL-1β; furthermore, IL-1β enhanced the vasoconstriction effect of phenylephrine (236).

The MetS has been shown to predict CVD events in hypertensive subjects independently of traditional risk factors (237). In hypertensive subjects, the MetS impairs total arterial compliance (238). Particularly, in untreated hypertension the MetS is associated independently with aortic stiffness, which was found to also be determined by central obesity, but not by BMI (239). When hypertensive subjects with and without the MetS were compared in relation to cardiovascular damage, this damage was statistically more frequent among the MetS group and, moreover, strongly related to increased low-grade inflammation and fibrosis present in this group (240). There is, therefore, increasing data that low-grade inflammation is connected with hypertension when the MetS is present.

2.4 DYSLIPIDEMIA, LOW-GRADE INFLAMMATION AND THE METABOLIC SYNDROME

Elevated triglycerides and decreased HDL-levels, the characteristic dyslipidemic factors of the MetS, are associated with low-grade inflammation (241, 242). IL-6 is capable of acting as an independent stimulator of triglycerides in the liver in animal models (243). Hypertriglyceridemia is associated with decreased adiponectin levels, even when it is present without the MetS (244). The liver is the main source of lipid regulation in the body and abundant fat accumulation in the liver is considered as a hepatic sign of the MetS (245). Of liver fat, 60% comes from non-esterified fatty acids, which are a result of lipolysis in adipose tissue or are hydrolyzed from lipoproteins at such a rate that they cannot be assimilated by adipose tissue, 25% comes from newly synthesized fatty acids and 15% comes from dietary chylomicrons (245). Non-alcoholic fatty liver disease (NAFLD) is strongly associated with obesity and insulin resistance; it has been observed that 70% of subjects with T2D, and even 95 % of those who are obese, have NAFLD (246). NAFLD is a strong predictor of the MetS, even in non-obese, non-diabetic subjects, and it can thus be considered an early sign of the MetS (247). In subjects with the MetS, the incidence of NAFLD is fourfold in men and 11-fold in women, compared to subjects without the MetS (248). The amount of fat accumulated in the liver is correlated with the quantity of visceral adipose tissue and with insulin resistance. In the insulin resistance state, increased hepatic triglyceride synthesis may result in the synthesis of very low-density lipoproteins (VLDL), which form highly atherogenic small dense lipoprotein particles, cholesterol-rich VLDL remnants and triglyceride-rich HDL particles (249). These HDL particles may be cleared in the kidneys, thus leading to decreased HDL levels (250). Thus, dyslipidemic features that are characteristic of the MetS are seen in NAFLD. Also adiponectin levels are decreased in

NAFLD. Furthermore, in experimental models there appears an amelioration of NAFLD with administration of adiponectin (251). In the case of low-grade inflammation, fat accumulation in the liver, insulin resistance and the MetS, there is no straight or direct causality but instead a complex network of probably genetic and as yet unknown factors which contribute to each other, making a dynamic continuing process (246). NAFLD is, however, closely related to the MetS and might be even a central factor in the pathophysiology of the dyslipidemia frequently seen in the MetS.

2.5 OTHER CONDITIONS ASSOCIATED WITH THE METABOLIC SYNDROME

There are several conditions which are associated with the MetS, even though they are not included in the diagnostic criteria of this syndrome. In addition to the previously mentioned NAFLD, there is evidence that polycystic ovarian syndrome (PCOS), hypogonadism, obstructive sleep apnea, prothrombotic state, hyperuricemia, depression and Alzheimer's disease are also associated with the MetS. Among subjects with metabolic disorders, there are observed cancers of reproductive and gastrointestinal systems more often than in the general population (252).

PCOS is accompanied with increased T2D risk as well, with increased risk for CV risk factors (253,254). Hyperinsulinemia has been speculated to be a common pathogenetic factor behind PCOS, with which the MetS commonly appears (255). Furthermore, increased visceral adipose tissue has been observed in PCOS and inflammatory cytokines seem to stimulate androgen production of ovaries affected by PCOS (256). Though further research is definitely needed, there is significant evidence suggesting that PCOS might occur in conjunction with the MetS.

Hypogonadism is associated with the MetS and T2D (257). In men who were unaware of their hormone concentrations, low levels of testosterone as well as sex-hormone binding globulin were independent risk factors for the development of the MetS (258). In particular, visceral adiposity appears together with hypogonadism (259). Furthermore, there is evidence showing that features of the MetS may be ameliorated and levels of the pro-inflammatory cytokines may be decreased with testosterone replacement therapy (260, 261).

Obstructive sleep apnea is firmly connected with obesity. Similarly, there is an association between obstructive sleep apnea and insulin resistance, as well as increased levels of inflammatory markers. The prevalence of the MetS is high among subjects with this disorder (262, 263).

Recently several groups have reported their findings about the associations between carcinogenesis, the MetS, visceral adiposity and insulin resistance (264, 265, 266). Furthermore, there are results suggesting that both visceral adiposity and the MetS might be associated with more progressive tumors and reduced survival (265, 266).

The underlying pathological mechanisms connecting these conditions which have been reported to be associated with the MetS are not simple nor solved. Inflammatory aspects and especially visceral adiposity are thought to be important contributors in this network of several diseases. However, much additional knowledge is needed before there is solid

proof of these connections and even more before it will be possible to solve the multiple pathways which mediate these associations.

2.6 SMOKING IN RELATION TO THE METABOLIC SYNDROME AND LOW-GRADE INFLAMMATION

Smoking is a well known risk factor for CVD. Smoking is also correlated with insulin resistance and the MetS, and smokers seem to be at increased risk of T2D (26,267- 271). With smoking, the risk for complications of diabetes (such as neuro-, nephro- and retinopathy) increases as well (269). Smoking has harmful effects on body fat distribution with increased centrally located fat, even dose-dependently (272, 273). Furthermore, there is evidence that smoking is positively associated with the increase of total body fat (273). Increased levels of inflammatory markers have been observed in smokers, even though in studies concerning acute smoking there has also been found suppression of inflammatory cytokines (274, 275). Moreover, among smokers, adiponectin levels are shown to be decreased (181, 276, 277). Additionally, there are results that suggest that adiponectin levels are elevated and pro-inflammatory markers decrease with smoking cessation (278 - 281). However, levels of CRP have been found to be significantly elevated among ex-smokers even 10 to 20 years after quitting, which may suggest ongoing low-grade inflammation in these former smokers (27).

The association between smoking and body weight is complicated. Smokers often seem to have lower body weight compared to non-smokers (272, 282). However, there are results from a male study population that show waist circumference being relatively larger and hip circumference smaller in smokers, compared to non-smokers (272). Furthermore, with smoking cessation and subsequent weight gain, the increase in WHR is not as large as expected given the added weight, thus indicating that fat in smokers probably is more centrally located (272). Additionally, that finding leads to speculation that smokers not only have increased abdominal fat, but also probably lose muscle (272). In another study conducted among the Swiss population, an increase in waist circumference was found in both genders who smoked. Moreover, smokers had more total body fat compared to non-smokers; this finding was especially pronounced in females (273).

Estrogen levels are lower in female smokers (283). With estrogen decrease during menopause, there appears an increase in visceral fat mass (284, 285). Thus, smoking is thought to contribute to an accumulation of centrally located fat via estrogen; this could partly explain the harmful association of visceral fat with smoking in females (284). In males, there are similar findings of lower levels of testosterone, as appears with aging, being associated with more centrally accumulated fat (286). Smokers have higher levels of cortisols. Interestingly, between active and passive smokers there were not found any differences in steroid hormones (287,288, 289). Cortisol levels are also known to influence central fat accumulation (290). Smoking is often accompanied with other deleterious habits like physical inactivity, alcohol consumption and unhealthy diet, which may contribute to a degree of obesity (291). With growing evidence that increases in both total body fat and centrally located fat accelerate low-grade inflammation, it seems definitive that the

deleterious effects of smoking are mediated partly through inflammatory changes. Still, further research is needed to determine the causal pathways.

2.7 THE ROLE OF GENDER IN METABOLIC DISEASES

Though men are known to be at greater risk of CVD compared to women in the general population, it seems to be totally the opposite case among diabetic subjects. As a result of a large Australian meta-analysis, there was observed to be a 50% higher relative risk of fatal coronary heart disease in diabetic women than in men (292). There are similar results in several studies where diabetic women seem to be at higher risk of major as well as all CVD events, compared to diabetic men, even to the extent that the gender-related advantage in non-diabetic women compared to non-diabetic men seems to be completely lost (35,36). The MetS appears to be a stronger predictor of CVD in women than in men (32). The effect of the MetS on left ventricular function and hypertrophy is greater in women than in men among hypertensive subjects (33). In the Hoorn Study, it was observed that impaired glucose tolerance and T2D are associated with increased left ventricular mass in women, but not in men (293).

CRP levels seem to be a better predictor of T2D in women than in men (34, 294). In another study, a similar gender difference between CRP and early progression of carotid atherosclerosis was found (295). In subjects with T2D, both leptin and IL-1Ra levels were significantly elevated in women, compared to men (296). Adiponectin concentrations in healthy subjects are constantly higher in women than in men (166). This development in adiponectin concentrations seems to begin in childhood, with increasing difference after the progression of puberty in boys (297). Furthermore, lower adiponectin levels were also found in obese children, compared to normal weight children, in relation to the degree of obesity (297). Hypoadiponectinemia has been linked with obesity, T2D and CVD. Because of evidence that adiponectin levels decrease with increased abdominal obesity, changes in fat distribution have been suggested as an explanation for the gender differences regarding these diseases and adiponectin, and probably also wider low-grade inflammation (166, 168).

The observation that CVD begins to appear relatively more in women in menopause, and the well-known fact that women have similar CVD prevalence rates as men around ten years greater in age, has led to the idea that estrogen provides protection for women against metabolic diseases (60,298, 299). These ideas could also be supported by changes in fat distribution with aging, while decreases in estrogen levels are associated with centrally located fat (284, 285). In the Health in Men Study, low testosterone levels were found to predict CVD mortality (300). Similar results were found also in meta-analyses of 70 studies. Furthermore, testosterone replacement therapy has been useful in reducing risks of CVD (301). However, it is not possible to present any causality in the involvement of sex steroid hormones and metabolic diseases until further research has been done.

In any case, it seems clear that there are gender-specific risks for CVD and other metabolic diseases. Continuous further research is warranted to solve problems, especially including women's heart disease diagnosis and treatment; thus far, there are still several unsolved problems in this question of gender differences in metabolic diseases (302, 303).

2.8 CONTROVERSIES REGARDING THE METABOLIC SYNDROME

As mentioned above, there exist several theories with unanswered questions about the pathophysiology of the MetS. Uniform criteria for the MetS are still under debate and the different definitions identify different individuals as having the MetS (78). Moreover, there is disagreement about the usefulness of this cluster in predicting the risk for CVD or T2D, especially compared to established predictive scores like Diabetes Risk Score (5, 304), These issues have raised criticism about the term "syndrome", which refers to unified pathophysiology and the MetS to be a special "diagnosis", especially when the treatment of this syndrome is nothing else but the treatment of its components (305). The debate about the existence of the MetS is ongoing, with statements for and against it (89, 305, 306, 307). At the same time, with the current epidemic of obesity, there is a great need for better tools to identify individuals with increased risk of CVD and T2D.

3 Aims of the study

The aim of this study was to obtain new, gender-specific information about the association of adiponectin and low-grade inflammation with factors that often precede the metabolic syndrome and to get information about these markers in relation to the course of the metabolic syndrome.

More specifically, this study was intended to address the following objectives:

1. To study possible gender differences in adiponectin and markers of low-grade inflammation within a relative change of BMI from youth to middle-age.

2. To examine from a gender-specific point of view the associations between smoking and low-grade inflammation measured by adiponectin and hs-CRP.

3. To investigate gender differences as related to low-grade inflammation and insulin resistance in hypertensive subjects with the metabolic syndrome.

4. To study the associations between adiponectin and low-grade inflammation in relation to the course of the metabolic syndrome, and to assess gender differences related to this question.

4 Subjects and methods

4.1 STUDY POPULATION

All inhabitants of the town of Pieksämäki born in 1942, 1947, 1952, 1957 and 1962 (n=1294), without any excluding criteria, were invited for a health check-up during the years 1997-1998 and again in the years 2003-2004. Written invitations were mailed according to the civil register and repeated two separate times. Of all invited subjects, 923 (71.3%, 411 men and 512 women) participated in the first health check-up, and 681 subjects of them participated in the second check-up. The study population is presented by gender and year of birth in Figure 2.

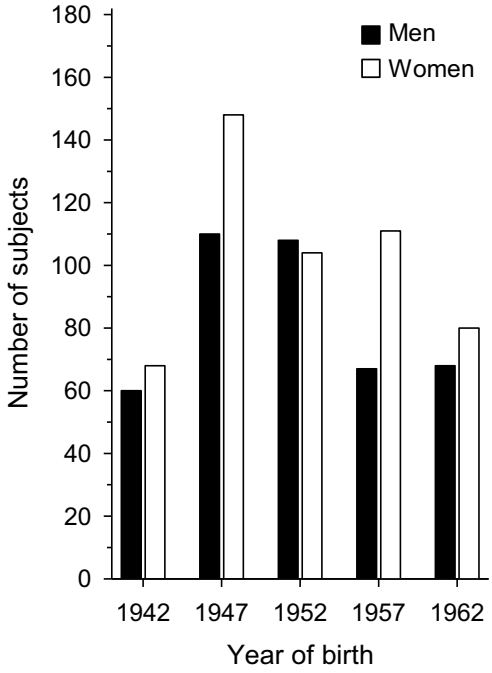


Figure 2. Study population (n=923) by year of birth and gender

In Study I, from the first check-up, 18 subjects of 923 with possible acute inflammatory condition (hs-CRP ≥ 10 pg/ml) and two subjects with missing weight information as a youth were excluded. Thus, the final study population consisted of 903 subjects (403 men and 500 women).

In Study II, of the 923 subjects in the first check-up, 64 diabetic subjects as well as 18 subjects (7 men, 11 women) with hs-CRP ≥ 10 pg/ milliliter, who might therefore had some acute inflammatory condition, were excluded. The final non-diabetic study population consisted of 841 subjects (365 men and 476 women).

In Study III, all subjects from the first check-up with systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or receiving antihypertensive medication were included, while subjects with hs-CRP ≥ 10 pg/ml (n=18) were excluded, due to possible acute inflammatory condition. Thus, the final study population included 551 subjects (278 men and 273 women).

In Study IV, the study population consisted of 680 subjects (284 men and 396 women) who participated in both check- ups (n=681), except one subject with hs-CRP ≥ 30 pg/ml, who probably had some acute inflammatory condition. Both male and female subjects were divided into four groups, according to their MetS status at the first and second check-ups: "No MetS" (= subjects who did not have MetS at either point of measurement), "Incident MetS" (= subjects who did not have MetS at the first point of measurement but in whom it was expressed at the second point of measurement), "Persistent MetS" (= subjects who had MetS both at the first and the second point of measurement), and "Resolute MetS" (= subjects who had MetS at the first point of measurement but not at the second one).

4.2 CLINICAL METHODS, QUESTIONNAIRES AND INTERVIEWS

All subjects completed a questionnaire about their medical history and their current medical condition. They were interviewed and examined by a nurse who was specially trained for this task by a researcher physician in 1997.

Subjects were asked about their smoking habits, alcohol consumption and physical activity. Subjects who smoked on a daily basis were considered to be current smokers. All subjects who used alcohol, regardless of amount, were considered to be alcohol users. Subjects exercising at least three times a week with a minimum of 30 minutes a session were considered to be physically active.

Subjects were also asked about their height and weight at the age of 20 years, as well as the length and degree of their education. Total education of ≤ 10 years was referred to as "lower education" and thus lower socio-economical status in Study I.

Weight while wearing light clothing and height were measured to an accuracy of 0.1 kg and 0.5 cm, respectively. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. The relative change in BMI (Study I) was calculated as the BMI at the check-up divided by BMI at the age of 20 years. Waist circumference was measured from the midpoint between the lateral iliac crest and the lowest rib to an accuracy of 0.5 cm.

Blood pressure (BP) was measured with a mercury sphygmomanometer, after the subject had 15 minutes of rest, in a sitting position. The measurement was repeated after five minutes. The mean of the two measurements was used in the analyses, except in Study II where the second reading was used in analyses.

4.3 LABORATORY MEASUREMENTS AND CALCULATIONS

Fresh blood samples were drawn after an overnight (12 hours) fast. Plasma was separated by centrifugation for the determination of fasting insulin, and the samples were frozen immediately to -20 . The frozen samples were transported weekly to Kuopio University Hospital and stored at -70 until adiponectin, interleukin-1 receptor antagonist (IL-1Ra), interleukin-1β (IL-1β) and high-sensitivity C-reactive protein (hs-CRP) were analyzed in 2003, contemporaneously in the scientific laboratory of the University of Kuopio.

Plasma insulin was determined using the Phadesph Insulin radioimmunoassay (RIA) 100 method (Pharmacia Diagnostics AB, Uppsala, Sweden) in the scientific laboratory of Kuopio University Hospital.

Plasma glucose concentration was measured by an automated colorimetric method (Peridochrom Glucose GOD-PAP, Boehringer, Germany). Serum cholesterol and triglycerides were measured in fresh serum samples by enzymatic colorimetric methods (CHOD-PAP, GPO-PAP, Boehringer Mannheim GmbH, Germany). Serum high density lipoprotein (HDL) cholesterol was measured by the same method after precipitation of low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol with phosphotungstic acid and magnesium. Glucose and lipids were determined in the routine laboratory of Pieksämäki District Hospital.

Serum hs-CRP was measured with an Immulite analyzer and a DPC high-sensitivity CRP assay (DPL, Los Angeles, CA, USA). Serum adiponectin was determined with an enzyme immunoassay (Human Adiponectin Elisa Kit, B-Bridge International INC, Mountain View, CA, USA). Plasma concentrations of IL-1β and IL-1Ra were determined using high-sensitivity calorimetric ELISA Kits HSLB 50 and DRA00 form R&D systems (Minneapolis, MN, USA). The sensitivities of the assays were 0.1 pg/ml and 22 pg/ml, respectively.

An oral glucose tolerance test was performed, according to the WHO protocol, using a 75g glucose load.

The quantitative insulin sensitivity check index (QUICKI) (94), which was used as a marker of insulin sensitivity (Study IV), was calculated as follows: QUICKI = 1/(log FPI + log FBG), where FPI = fasting plasma insulin level expressed as mU/l, and FBG = fasting plasma glucose level expressed as mg/dl.

4.4 DETERMINATION OF THE METABOLIC SYNDROME

In this study, the MetS was determined according to the NCEP/ATP III criteria: subjects with three or more of the following components were classified as having MetS: 1) increased waist circumference (≥ 102 cm [≥40 in] for men and ≥88 cm [≥35 in] for women), 2) elevated fasting total triglycerides (≥1.7 mmol/l [≥150 mg/dl] or treatment for dyslipidemia), 3) low fasting serum high-density lipoprotein (HDL) cholesterol (<1.03 mmol/l [<40 mg/dl] for men and <1.29 mmol/l [<50 mg/dl] for women or treatment for dyslipidemia), 4) systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or the use of antihypertensive medication, and 5) fasting plasma glucose ≥5.6 mmol/l [≥ 100 mg/dl] or the use of medication for hyperglycemia.

4.5 STATISTICAL ANALYSIS

The results are expressed as means with standard deviations (SD), or as counts with percentages.

In Study I, a statistical comparison between the genders was performed by t-test or bootstrap-type t-test, when appropriate. Statistical significance for the hypotheses of linearity was evaluated by using generalized linear models with appropriate distribution and link function.

In Study II, statistical comparisons among the groups were performed by t-test or bootstrap-type t-test, when appropriate. Bootstrap-type ANCOVA was used to determine BMI and age-adjusted values. The normality of variables was evaluated by Shapiro-Wilk test. Confidence intervals (CI) were obtained by bias-corrected bootstrapping (5000 replications).

In Study III, the CIs for ORs (Odds Ratio) were obtained by bias-corrected bootstrapping (5000 replications). Statistical comparisons between the groups were performed by chi-square test, t-test or bootstrap-type t-test, as appropriate. Logistic regression models were used to investigate the linear association between the MetS and gender-specific tertiles of insulin, hs-CRP, adiponectin and inflammatory cytokines. Adjustments were made for age, physical activity, smoking and use of alcohol in model 1, and BMI was added for model 2. The normality of variables was evaluated by Shapiro-Wilk statistics. The Clopper-Pearson method was used to calculate the CI for the prevalence rate.

In Study IV, a statistical comparison between groups was made by t-test, bootstrap-type t-test, permutation test, chi-square test or Fisher exact test, when appropriate. Age, change in BMI, smoking status and physical activity were added into the model as covariates. The 95 per cent confidence intervals for the most important outcomes were obtained by bias-corrected bootstrapping.

Data processing and statistical analyses were performed using SPSS (v.11.5) and STATA (v.11.1) for Windows.

4.6 ETHICAL CONSIDERATIONS

In the invitation letters and in the first interview, all the subjects were informed about the aims and methods of the study. All the participants gave written consent.

Questionnaires and the data are confidentially stored in the archives of the Unit of Family Practice in Central Finland Central Hospital.

The study protocol was approved by the Ethics Committee of Kuopio University Hospital and the University of Kuopio in 1996.

5 Results

5.1 CHARACTERISTICS OF THE STUDY POPULATION

The basic demographic, clinical, biochemical and lifestyle characteristics of the study subjects are presented in Table 2. The presence of the MetS according to BMI, separately in men and women in the study population, is shown in Figure 3.

Table 2. Demographic, clinical, biochemical and lifestyle characteristics of the study population

Variables	**Men (N=411) Mean (SD)**	**Women (N=512) Mean (SD)**	**P-value**
Demographic			
Age, years	46 (6)	46 (6)	
Body mass index, kg/m²	26.7 (3.8)	26.3 (4.9)	0.15
Waist, cm	93.8 (10.6)	83.3 (12.2)	< 0.001
Clinical			
Blood pressure, mmHg			
Systolic	137 (17)	131 (17)	< 0.001
Diastolic	84 (10)	79 (9)	< 0.001
Biochemical			
HDL cholesterol, mmol/l	1.3 (0.3)	1.5 (0.3)	< 0.001
Triglycerides, mmol/l	1.7 (1.3)	1.2 (0.6)	< 0.001
FP-glucose, mmol/l	5.9 (0.6)	5.6 (0.5)	< 0.001
FP-insulin, mU/l	10.7 (5.9)	9.8 (6.5)	< 0.001
Hs-CRP, pg/ml	1.3 (1.5)	1.5 (1.7)	0.035
IL-1β, pg/ml	0.61 (0.43)	0.61 (0.47)	0.94
IL-1Ra, pg/ml	172 (131)	192 (167)	0.16
Adiponectin, µg/ml	4.9 (2.7)	7.9 (4.4)	< 0.001
Lifestyle			
Number of current smokers (%)	136 (33)	112 (22)	< 0.001

HDL= high density lipoprotein, FP= fasting plasma, hs-CRP= high-sensitivity C-reactive protein, IL-1β= Interleukin-1 beta, IL-1Ra= Interleukin-1 Receptor antagonist, current smoker= a daily smoker

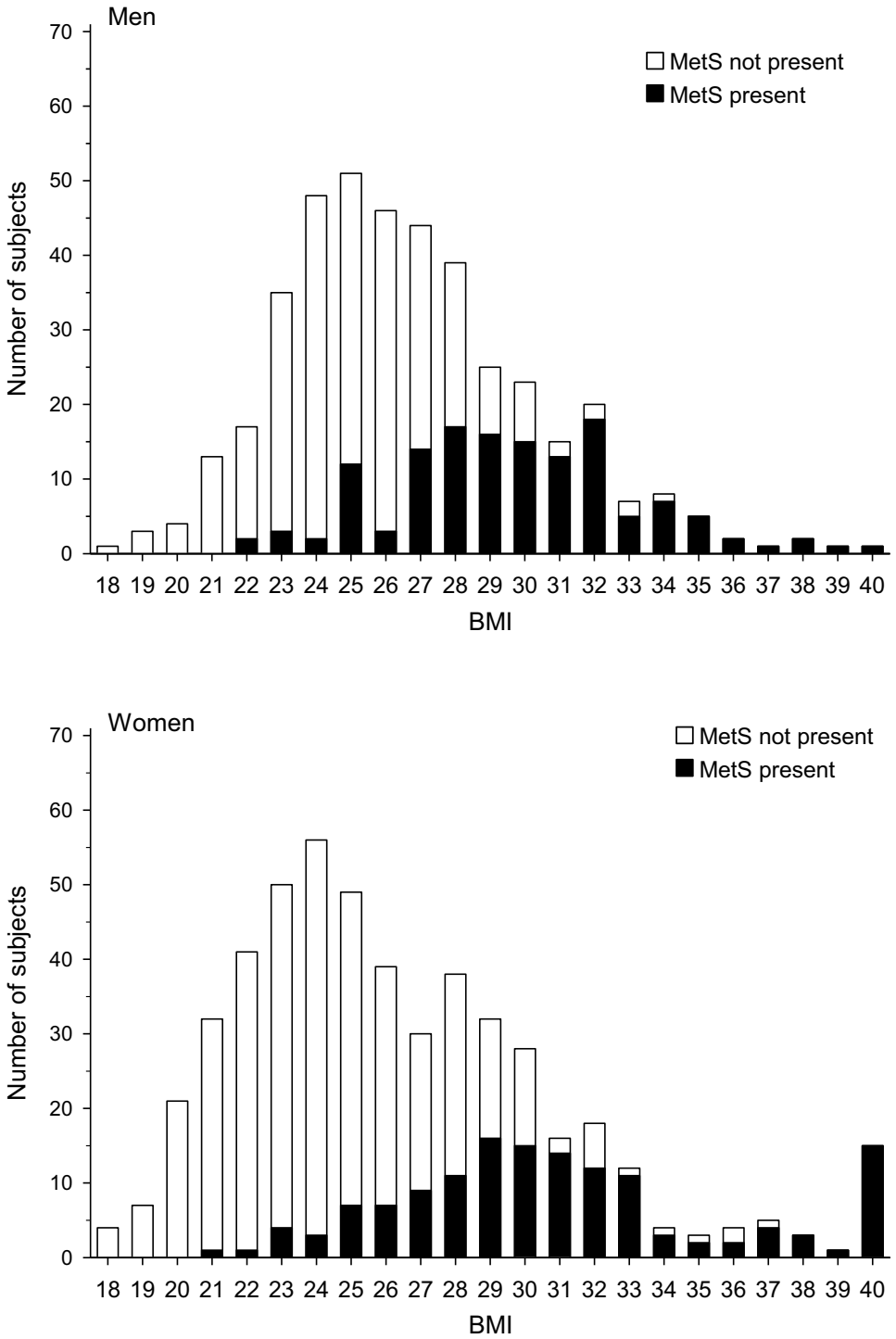


Figure 3. The number of male and female study subjects, according to BMI (kg/m²) and the presence of the MetS

5.2 INTERRELATION BETWEEN ADIPONECTIN AND INFLAMMATORY MARKERS

In correlations, adjusted for age and gender, among measured inflammatory markers there were statistically significant negative correlations between adiponectin and IL-1Ra ($p<0.001$) and adiponectin and hs-CRP ($P=0.020$). A statistically significant positive correlation was found between IL-1Ra and hs-CRP ($p<0.001$) (Table 3).

Table3. Correlations between adiponectin, interleukin-1 receptor antagonist (IL-1Ra), interleukin-1 beta (IL-1β) and high- sensitivity C-reactive protein (hs-CRP) adjusted for age and gender

	Adiponectin	**IL-1Ra**	**IL-1β**	**hs-CRP**
Adiponectin		-0.200 (p<0.001)	0.014 (p=0.72)	-0.090 (p=0.020)
IL-1Ra	-0.200 (p<0.001)		0.016 (p=0.684)	0.343 (p<0.001)
IL-1β	0.014 (p=0.72)	0.016 (p=0.68)		-0.001 (p=0.99)
hs-CRP	-0.090 (p=0.020)	0.343 (p<0.001)	-0.001 (p=0.99)	

5.3 GENDER DIFFERENCES IN THE ASSOCIATION OF ADIPONECTIN AND LOW-GRADE INFLAMMATION WITH THE RELATIVE CHANGE IN BODY MASS INDEX FROM THE AGE OF 20 YEARS TO MIDDLE AGE (STUDY I)

At the age of 20 years, the mean weight was 71 (SD 9) kg in men and 57 (SD 8) kg in women. The means of BMI were 22.6 (SD 2.5) kg/m² and 21.2 (SD 2.7) kg/m², respectively ($p<0.001$ between genders). The mean increase in weight from the age of 20 years to middle-age was 12.8 (SD 11.2) kg in men and 13.9 (SD 11.9) kg in women ($p=0.16$ between genders). There was no significant gender difference in BMI in middle-age. The demographical, clinical and biochemical charasteristics of the study subjects at the mean age of 46 years are presented in Table 4.

The associations of adiponectin, IL-1Ra, IL-1β and hs-CRP were examined with the quartiles of the relative change in BMI from the age of 20 years to middle-age. There was no statistically significant difference in alcohol intake between the quartiles of the relative change in BMI in men or in women.

In men, a statistically significant linear association was observed between quartiles of the relative change in BMI and IL-1Ra and hs-CRP levels ($p< 0.001$ for linearity). This significance disappeared after adjusting for BMI in middle-age. (Table 5)

In women, a statistically significant negative linear association was observed between quartiles of the relative change in BMI and levels of adiponectin. There were also significant positive linear associations between the change in BMI and levels of IL-1Ra and hs-CRP ($p <0.001$ for linearity). After an adjustment for BMI in middle-age the negative association between adiponectin and the relative change in BMI remained significant ($p< 0.001$ for linearity), and the positive associations between the change in BMI and levels of IL-1Ra and hs-CRP were statistically significant ($p<0.05$). (Table 5)

Associations between socio-economical status and relative change of BMI were also examined. The dichotomy between lower and higher socio-economical status was made according to total years of education (lower education ≤ 10 years). In men, there was found no association between the socio-economical status and the relative change in BMI; the proportion of men with higher socio-economical status (n=90) varied from 19% to 26% across the tertiles of weight increase (p=0.30 for linearity). In women, there was seen a statistically significant difference between the socio-economical status and the relative change in BMI. The proportion of women with higher socio-economical status (n=193) decreased from 46% to 28% across the tertiles of relative weight increase (p=0.003 for linearity).

Table 4. Demographic, clinical and biochemical characteristics of the Study I population in middle age

Characteristics	**Men** **N=403** **Mean (SD)**	**Women** **N=500** **Mean (SD)**	**P-value**
Demographic			
Age, years	46 (6)	46 (6)	0.37
Height, cm	177 (6)	163 (6)	<0.001
Weight, kg	82 (12)	70 (13)	<0.001
Body mass index, kg/m²	26.7 (3.7)	26.3 (4.9)	0.14
Clinical			
Blood pressure, mmHg			
Systolic	137 (17)	131 (17)	<0.001
Diastolic	84 (10)	79 (9)	<0.001
Biochemical			
Total cholesterol, mmol/l	5.8 (1.0)	5.6 (1.0)	<0.001
HDL cholesterol, mmol/l	1.3 (0.3)	1.5 (0.3)	<0.001
Total triglycerides, mmol/l	1.7 (1.3)	1.2 (0.6)	<0.001
Fasting plasma glucose, mmol/l	5.9 (0.6)	5.6 (0.5)	<0.001

HDL= high density lipoprotein

Table 5. The associations of adiponectin, high-sensitivity C-reactive protein (hs-CRP), interleukin-1 beta (IL-1β) and interleukin-1 receptor antagonist (IL-1Ra) with the relative change quartiles in body mass index (BMI, kg/m²) from the age of 20 years to middle age, in both genders

Variables	**Relative change quartiles in BMI from 20 years to middle age**				**P-value for linearity**	
	1.	**2.**	**3.**	**4.**	**Crude**	**Adjusted †**
Men						
Number	99	102	102	100		
Relative change in BMI, range	0.78–1.07	1.07-1.17	1.17-1.27	1.27-1.79		
Adiponectin, µg/ml, mean (SD)	5.32 (2.95)	4.83 (2.29)	4.66 (2.40)	4.66 (3.10)	0.077	0.20
IL-1β, pg/ml, mean (SD)	0.62 (0.49)	0.61 (0.30)	0.64 (0.60)	0.57 (0.23)	0.60	0.57
IL-1Ra, pg/ml, mean (SD)	137 (85)	155 (72)	176 (104)	221 (206)	<0.001	0.57
hs-CRP, pg/ml, mean (SD)	0.84 (0.98)	1.34 (1.61)	1.40 (1.48)	1.72 (1.74)	<0.001	0.35
Women						
Number	126	128	127	119		
Relative change in BMI, range	0.83-1.10	1.10-1.22	1.22-1.36	1.36-2.24		
Adiponectin, µg/ml, mean (SD)	9.11 (5.39)	8.39 (4.58)	7.09 (3.63)	6.85 (3.50)	<0.001	<0.001
IL-1β, pg/ml, mean (SD)	0.58 (0.38)	0.58 (0.24)	0.62 (0.32)	0.66 (0.78)	0.14	0.16
IL-1Ra, pg/ml, mean (SD)	128 (62)	140 (75)	200 (153)	305 (251)	<0.001	0.032
hs-CRP, pg/ml, mean (SD)	0.87 (1.10)	1.07 (0.99)	1.70 (1.66)	2.34 (1.90)	<0.001	0.029

† Adjusted for BMI in middle age.

5.4 GENDER DIFFERENCE AMONG SMOKING, ADIPONECTIN AND HS- CRP (STUDY II)

Among 365 men and 476 women, there were 125 (34%) male and 104 (22%) female smokers (p<0.001 between genders). On average, men had smoked for 22 years (95% CI 20-30 years) and women for 20 years (95% CI 15-25 years, p=0.001 between genders). The median number of cigarettes per day was 14 (95% CI 9-20) in men and 10 (95% CI 6-14) in women (p< 0.001 between genders).

Demographic, clinical and biochemical characteristics of the study population divided by gender and smoking are presented in Table 6.

In smoking males, hs-CRP levels were significantly higher compared to non-smoking males (1.59±1.71 pg/ml vs. 1.17±1.41 pg/ml, p=0.018). This association remained significant after adjusting for age and BMI (p=0.0056). In adiponectin, no significant association related to smoking was seen in men. (Figure 4)

In smoking females, adiponectin levels were significantly lower compared to non-smoking females (6.94 ± 3.27 μg/ml vs. 8.27 ± 4.72 μg/ml, p=0.0017), with the association remaining significant after adjustment for age and BMI (p=0.0061), but no significant association between smoking and hs-CRP was seen in women. (Figure 4)

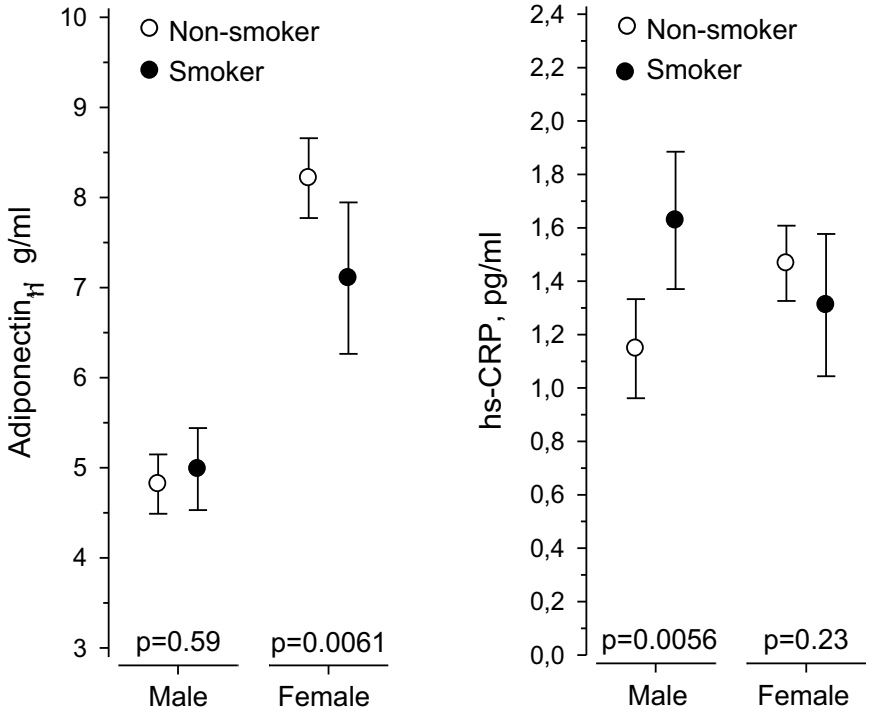


Figure 4. Adiponectin and hs-CRP levels and smoking by gender, adjusted for BMI and age

Table 6. Demographic, clinical, and biochemical characteristics of the Study II population divided by gender and smoking

Variables	Men (*n*=365)			Women (*n*=476)		
	Non-smokers (*n*=240) M (SD)	Smokers (*n*=125) M (SD)	*p*-value	Non-smokers (*n*=372) M (SD)	Smokers (*n*=104) M (SD)	*p*-value
Demographic						
Age (years)	47 (6)	46 (7)	0.46	47 (6)	45 (6)	0.022
BMI (kg/m²)	26.5 (3.1)	26.1 (3.8)	0.34	26.0 (4.5)	25.8 (4.8)	0.81
Waist circumference (cm)	93 (9)	93 (10)	0.63	83 (11)	82 (12)	0.80
Clinical						
Blood pressure (mmHg)						
Systolic	135 (16)	137 (17)	0.37	131 (17)	127 (16)	0.023
Diastolic	83 (10)	83 (10)	0.89	80 (9)	78 (9)	0.037
Biochemical						
FS-cholesterol (mmol/l)	5.8 (1.0)	5.8 (1.1)	0.88	5.6 (1.0)	5.6 (0.9)	0.65
HDL cholesterol (mmol/l)	1.30 (0.29)	1.29 (0.30)	0.62	1.52 (0.34)	1.45 (0.31)	0.031
Triglycerides (mmol/l)	1.54 (1.0)	1.54 (0.82)	0.96	1.16 (0.56)	1.25 (0.67)	0.21
FP-glucose (mmol/l)	5.8 (0.5)	5.8 (0.5)	0.98	5.6 (0.5)	5.5 (0.4)	0.053
2-hour glucose (mmol/l)	5.4 (1.4)	5.2 (1.3)	0.089	5.8 (1.2)	5.2 (1.3)	0.003
FP-insulin (mμ/l)	10.0 (4.7)	9.7 (4.1)	0.57	9.6 (6.3)	9.1 (4.1)	0.38

cm= centimeter; FP= fasting plasma; FS=fasting serum; HDL=high-density lipoprotein; mmHg=millimeters of mercury; mmol/l=millimoles/liter; mμ/l= microliter (0.000001 liter)/liter

5.5 GENDER DIFFERENCES RELATED TO THE METABOLIC SYNDROME AND LOW-GRADE INFLAMMATION IN SUBJECTS WITH ELEVATED BLOOD PRESSURE (STUDY III)

Subjects using antihypertensive drugs or with systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg (278 men, 273 women) were included in this study. There was no statistically significant gender differences in the use of antihypertensive medication (14.4% of men, 14.7 % of women, p=0.930 between genders). The majority of antihypertensive drugs used were ACE-inhibitors and β-blockers with no gender differences. Demographic, clinical, biochemical and lifestyle factors of the study subjects are shown in Table 7.

Table 7. Demographic, clinical, biochemical and lifestyle factors of the Study III subjects

Variables	**Men (N=278)**	**Women (N=273)**	**p-value**
Demographic			
Age, years	47 (6)	48 (6)	0.38
Age distribution, years	36-57	36-57	NS
Body mass index, kg/m²	27.1 (3.8)	27.1 (5.2)	0.98
Waist circumference, cm	95 (11)	85 (13)	<0.001
Clinical			
Blood pressure, mmHg			
Systolic	146 (15)	144 (14)	0.10
Diastolic	88 (9)	85 (8)	<0.001
Medication for hypertension (%)	40 (14)	40 (15)	0.93
Medication for hyperlipidemia (%)	12 (4.4)	5(2.0)	0.092
Medication for diabetes (%)	6(2.0)	7(3.0)	0.75
Biochemical			
Total cholesterol, mmol/l	5.9 (1.1)	5.7 (1.0)	0.11
HDL cholesterol, mmol/l	1.3 (0.3)	1.5 (0.4)	<0.001
Triglycerides, mmol/l	1.7 (1.4)	1.3 (0.6)	<0.001
FP-glucose, mmol/l	6.0 (0.7)	5.7 (0.6)	<0.001
Lifestyle			
Number of current smokers (%)	94 (34)	52 (19)	<0.001
Number of alcohol users (%)	243 (88)	212 (78)	<0.001
Number of physically active (%)	87 (31)	78 (27)	0.48

HDL = high density lipoprotein; FP = fasting plasma (mean, SD in parentheses for continuous variables; number of subjects, percentage in parentheses for dichotomous variables)

The MetS, as defined by NCEP criteria, was observed in 35% (95% CI: 30% to 41%) of men and 34% (95% CI: 29% to 40%) of women (p=0.84 between genders). There were no statistically significant gender differences in the mean BMI, regardless of whether the subjects had the MetS (30.0± 3.8 kg/m² in men vs.30.9±5.1 kg/m² in women, p=0.20 between

genders) or not (25.6±2.7 kg/m² in men vs. 25.2±4.0 kg/m² in women, p=0.27 between genders).

The difference in adiponectin levels between men and women without the MetS was -3.85µg/ml (95%CI -4.72 to -3.10, p<0.001) and with the MetS -2.53µg/ml (CI 95% -3.44 to -1.68, p<0,001), respectively. Otherwise there were no gender differences if the MetS was not present. Among subjects with the MetS, hs-CRP level was 0.67 pg/ml (95% CI 0.13 to 1.17, p=0.013) and IL-1Ra level was 77 pg/ml (95% CI 17 to 141, p=0.014) higher in women than in men. (Table 8)

Table 8. Insulin, hs-CRP and cytokines, according to the presence of the metabolic syndrome

Variables	**MetS not present**			**MetS present**		
	Men (n=181)	**Women (n=180)**	**p-value** †	**Men (n=97)**	**Women (n=93)**	**p-value** †
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
FP-insulin, mU/l	9.2 (4.4)	8.4 (2.8)	0.065	15.3 (7.8)	15.0 (12.4)	0.85
hs-CRP, pg/ml	1.32 (1.58)	1.25 (1.37)	0.65	1.68 (1.70)	2.35 (1.99)	0.013
Adiponectin, µg/ml	5.02 (2.50)	8.87 (4.84)	<0.001	4.11 (2.36)	6.64 (3.72)	<0.001
IL-1Ra, pg/ml	157 (81)	174 (147)	0.17	212 (208)	289 (242)	0.014

† Bootstrap-type t-test, MetS= metabolic syndrome defined by the NCEP criteria, FP= fasting plasma, hs-CRP= high sensitive C-reactive protein, IL-1Ra= interleukin 1-receptor antagonist

In the association between adiponectin and the MetS, a statistically significant gender difference was found; after adjustment for BMI, the OR for the MetS was 0.30 (CI 95% 0.14 to 0.67) in the highest tertile of adiponectin, compared to the lowest one in females (p=0.003), not being significant in males. In males, only level of fP-insulin was associated in a statistically significant manner for the risk of the MetS, (p<0.001), and the significance was also seen in females (p=0.013). (Table 9)

Table 9. Odds ratio (OR) for the presence of metabolic syndrome as defined by the NCEP criteria, according to the gender-specific tertiles of fasting plasma insulin, C-reactive protein, adiponectin and interleukin-1- receptor antagonist in men and women in two adjusted models

Variables	**Men**				**Women**			
	Model 1		**Model 2**		**Model 1**		**Model 2**	
	OR (95% CI)	**p-value†**	**OR (95% CI)**	**p-value†**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value†**
FP-insulin		<0.001		<0.001		<0.001		0.013
1st tertile	1.00‡		1.00		1.00		1.00	
2nd tertile	4.77 (2.01 to 11.34)		3.76(1.46 to 9.66)		4.61 (1.95 to 10.88)		3.15(1.27 to 7.80)	
3rd tertile	22.02(9.20 to 52.71)		5.98(2.20 to16.23)		17.71(7.54 to 41.59)		6.00(2.36 to15.2)	
hs-CRP		0.12		0.26		<0.001		0.22
1st tertile	1.00		1.00		1.00		1.00	
2nd tertile	1.58 (0.84 to 2.97)		0.98(0.45 to 2.11)		1.76 (0.87 to 3.55)		1.21(0.55 to 2.65)	
3rd tertile	1.65 (0.87 to 3.10)		0.63(0.28 to 1.42)		4.85 (2.47 to 9.52)		1.65(0.74 to 3.66)	
Adiponectin		<0.001		0.44		<0.001		0.003
1st tertile	1.00		1.00		1.00		1.00	
2nd tertile	0.32 (0.17 to 0.61)		0.67(0.30 to 1.47)		0.59 (0.32 to 1.09)		0.67(0.33 to 1.37)	
3rd tertile	0.25 (0.13 to 0.49)		0.73(0.33 to 1.61)		0.25 (0.13 to 0.50)		0.30(0.14 to 0.67)	
IL-1Ra		0.003		0.77		<0.001		0.068
1st tertile	1.00		1.00		1.00		1.00	
2nd tertile	1.68 (0.88 to 3.22)		0.94(0.43 to 2.06)		3.98 (1.88 to 8.43)		2.45(1.07 to 5.62)	
3rd tertile	2.61 (1.37 to 4.94)		1.12(0.52 to 2.44)		6.80 (3.25 to 14.21)		2.22(0.94 to 5.24)	

Model 1: adjusted for age, physical activity, smoking status and alcohol use.
Model 2: adjusted for age, physical activity, smoking status, alcohol use and BMI.
† P-value for linearity. ‡ Denominator of odds ratio

5.6 ASSOCIATION OF ADIPONECTIN AND LOW-GRADE INFLAMMATION WITH THE COURSE OF THE METABOLIC SYNDROME (STUDY IV)

In this study, 284 men and 396 women were first divided according to the presence of the MetS at the baseline and further divided into four groups, according to the presence of the MetS at follow-up. No MetS and Incident MetS groups, as well as Persistent MetS and Resolute MetS groups, were compared.

At baseline, 473 (70%) of the study subjects were not diagnosed with MetS. In the follow-up, MetS was present in 102 (22%) of these subjects. MetS was detected at baseline in 207 (30%) of the study subjects, but it had resolved in 51 (25%) of these subjects in the follow-up. No statistically significant baseline differences in alcohol consumption, education, physical activity or marital status were observed in either gender between the No MetS and Incident MetS groups or between the Persistent MetS and Resolute MetS groups.

The mean follow-up time was 6.5 (SD0.4) years. Mean weight increased by 1.6 kg (range:-19.9 - + 26.2) in men and by 2.47 kg (-18.0 - + 19.8) in women. The change in BMI was 0.51 kg/m² (-6.73 - + 7.66) in men and 0.92 kg/m² (-7.03 - + 7.97) in women.The baseline demographic, clinical and biochemical characteristics of the study population divided by the course of the MetS are shown in Table 10 (men) and Table 11 (women).

After adjustment for age, change in BMI, smoking and physical activity, the baseline adiponectin level was observed to be associated with the course of the MetS in a statistically significant manner: in subjects without the MetS at baseline, lower adiponectin levels were associated with Incident MetS ($p<0.001$), while in study subjects with the MetS at baseline, lower adiponectin levels were associated with persistence of the MetS ($p=0.026$). (Table 12)

Furthermore, when the MetS was not present at baseline, increased IL-1Ra and decreased IL-1β levels were associated with the Incident MetS ($p=0.004$ and $p=0.039$, respectively). In subjects with the MetS at baseline, higher IL-1Ra and hs-CRP concentrations were associated with persistence of the MetS ($p=0.044$ and $p=0.036$, respectively). (Table 12 and Figure 5)

Table 10. Baseline demographic, clinical and biochemical characteristics of the male Study IV population, according to the course of the MetS

Variable	MetS not present at baseline			MetS present at baseline		
	At follow-up		p-value	At follow-up		p-value
	No MetS	Incident MetS		Persistent MetS	Resolute MetS	
	n=148	n=40		n=75	n=21	
Demographic:						
Age, years, mean (SD)	46 (6)	47 (5)	0.13	49 (6)	46 (7)	0.094
Body mass index,kg/m²,mean (SD)	24.9(2.4)	26.0(2.2)	0.013	30.1(3.2)	28.0(2.8)	0.0017
Waist circumference, cm	88(7)	93(7)	<0.001	105(9)	97(8)	<0.001
Medication for hypertension (%)	7(5)	7(18)	0.006	16(21)	2(10)	0.35
Medication for hyperlipidemia (%)	0(0)	2(5)	0.044	10(13)	0(0)	0.11
Clinical:						
Blood pressure, mmHg, mean (SD)						
Systolic	133(15)	130(13)	0.29	144(16)	140(12)	0.37
Diastolic	81(9)	82(8)	0.59	89(9)	85(9)	0.084
Biochemical, mean (SD):						
FS-cholesterol, mmol/l	5.7(1.0)	6.0(1.0)	0.061	5.9(1.1)	5.8(1.2)	0.77
HDL cholesterol, mmol/l	1.39(0.28)	1.33(0.23)	0.20	1.15(0.23)	1.14(0.29)	0.89
Triglycerides, mmol/l	1.23(0.57)	1.49(0.62)	0.018	2.50(2.02)	2.04(0.7)	0.13
FP glucose, mmol/l	5.7(0.5)	5.8(0.6)	0.38	6.4(1.6)	6.2(0.5)	0.35
2-hour glucose, mmol/l	5.3(1.3)	5.1(1.4)	0.40	6.2(3.2)	6.0(1.6)	0.67
FP-insulin, mU/l	8.4(3.3)	9.5(2.8)	0.047	15.0(6.9)	10.4(4.4)	0.0031
QUICKI	0.345 (0.019)	0.336 (0.018)	0.018	0.316 (0.020)	0.330 (0.017)	0.004

NoMetS: MetS not present at the first or the second measurement,
Incident MetS: MetS not present at the first measurement but present at the second one,
Persistent MetS: MetS present at the first and the second measurement,
Resolute MetS: MetS present at the first measurement but not at the second one,
QUICKI: quantitative insulin sensitivity check index.
FS= fasting serum, HDL= high density lipoprotein, FP=fasting plasma

Table 11. Baseline demographic, clinical and biochemical characteristics of the female Study IV population, according to the course of the MetS

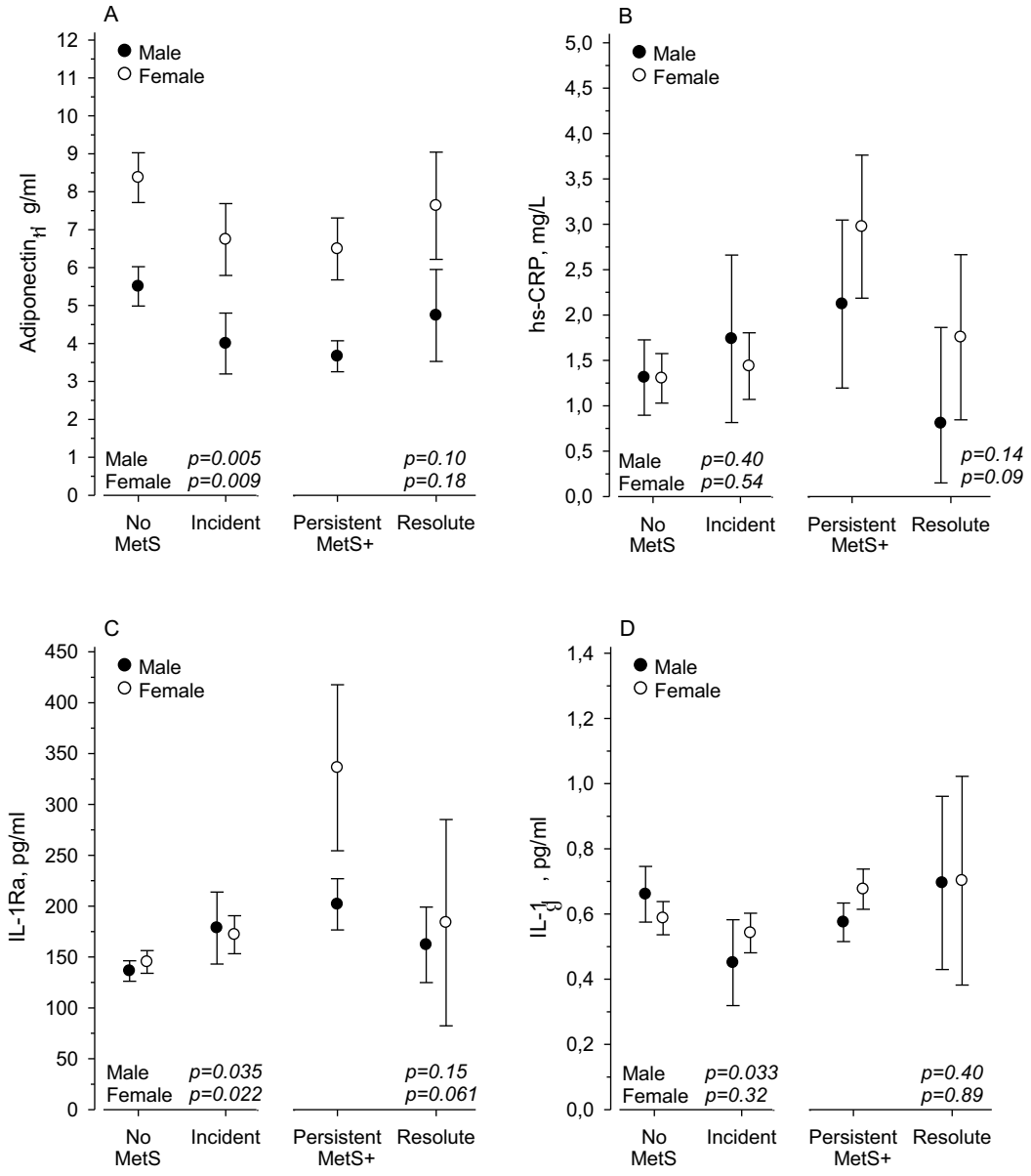
Variable	**MetS not present at baseline**			**MetS present at baseline**		
	At follow-up		**p-value**	**At follow-up**		**p-value**
	No MetS	**Incident MetS**		**Persistent MetS**	**Resolute MetS**	
	n=223	**n=62**		**n=81**	**n=30**	
Demographic:						
Age, years, mean (SD)	45 (6)	49 (6)	<0.001	48(6)	48 (6)	0.81
Body mass index,kg/m², mean (SD)	23.9 (3.0)	26.4(3.3)	<0.001	31.4(5.5)	28.4(4.4)	0.0081
Waist circumference, cm	77 (7)	84 (9)	<0.001	97(12)	89 (9)	0.003
Medication for hypertension (%)	7 (3)	8 (13)	0.006	19(23)	2 (7)	0.045
Medication for hyperlipidemia (%)	1 (0.7)	0 (0)	0.99	3(4)	1 (3)	0.99
Clinical:						
Blood pressure, mmHg, mean (SD)						
Systolic	125 (16)	134 (17)	<0.001	142(18)	139 (13)	0.48
Diastolic	76 (9)	81 (9)	<0.001	85(8)	82 (8)	0.081
Biochemical, mean (SD):						
FS-cholesterol, mmol/l	5.4 (0.8)	5.8 (0.9)	0.007	5.8(1.1)	5.8 (1.3)	0.97
HDL cholesterol, mmol/l	1.59 (0.30)	1.57 (0.35)	0.77	1.26(0.24)	1.34 (0.31)	0.22
Triglycerides, mmol/l	0.98 (0.38)	1.14 (0.57)	0.031	1.83(0.77)	1.34 (0.56)	<0.001
FP glucose, mmol/l	5.4 (0.4)	5.7 (0.5)	<0.001	6.1(0.6)	6.0 (0.5)	0.46
2-hour glucose, mmol/l	5.2 (1.1)	6.0 (2.4)	0.019	6.7(2.0)	6.1 (1.3)	0.12
FP-insulin, mU/l	8.0 (2.6)	9.1 (3.1)	0.011	15.5(3.6)	10.1 (3.9)	0.027
QUICKI	0.350 (0.017)	0.339 (0.017)	<0.001	0.319 (0.021)	0.333(0.018)	0.003

Incident MetS: MetS not present at the first measurement but present at the second one,
Incident MetS: MetS not present at the first measurement but present at the second one,,
Persistent MetS: MetS present at the first and the second measurement,
Resolute MetS: MetS present at the first measurement but not at the second one,
QUICKI: quantitative insulin sensitivity check index.
FS= fasting serum, HDL= high density lipoprotein, FP=fasting plasma

Table 12. The mean ratios of adiponectin, high-sensitivity C-reactive protein (hs-CRP), interleukin 1-Ra (IL-1Ra) and interleukin 1beta (IL-1β) levels presented between the No and Incident groups of metabolic syndrome (MetS) and between the Persistent and Resolute groups of MetS, after adjustment for age, change in BMI, smoking and physical activity

	Male **Ratio (95% CI)**	**Female** **Ratio (95% CI)**	**All** **Ratio (95% CI)**
Adiponectin			
No MetS vs. Incident MetS	1.38 (1.04 to 1.71)	1.24 (1.03 to 1.45)	1.27 (1.07 to 1.46) $^{p<0.001}$
Persistent MetS vs. Resolute MetS	0.77 (0.56 to 1.05)	0.85 (0.65 to 1.05)	0.80 (0.65 to 0.95) $^{p=0.026}$
hs-CRP			
No MetS vs. Incident MetS	0.75 (0.30 to 1.21)	0.91 (0.63 to1.19)	0.80 (0.56 to 1.05) $^{p=0.18}$
Persistent MetS vs. Resolute MetS	2.63 (0.02 to 6.70)	1.69 (0.59 to 2.80)	1.96 (1.01 to 3.34) $^{p=0.036}$
IL-1Ra			
No MetS vs. Incident MetS	0.76 (0.59 to 0.94)	0.84 (0.73 to 0.96)	0.83 (0.73 to 0.93) $^{p=0.004}$
Persistent MetS vs. Resolute MetS	1.25 (0.89 to 1.60)	1.83 (0.53 to 3.12)	1.54 (1.01 to 2.22) $^{p=0.044}$
IL-1β			
No MetS vs. Incident MetS	1.47 (1.02 to 2.02)	1.08 (0.91 to 1.26)	1.17 (1.01 to 1.34) $^{p=0.039}$
Persistent MetS vs. Resolute MetS	0.83 (0.32 to 0.99)	0.96 (0.48 to 1.45)	0.90 (0.60 to 1.21) $^{p=0.57}$

No MetS: MetS not present at the first or the second measurement
Incident MetS: MetS not present at the first measurement but present at the second one
Persistent MetS: MetS present at the first and the second measurement
Resolute MetS: MetS present at the first measurement but not at the second one



No MetS: MetS not present at the first or the second measurement
Incident MetS: MetS not present at the first measurement but present at the second one
Persistent MetS: MetS present at the first and the second measurement
Resolute MetS: MetS present at the first measurement but not at the second one

Figure 5. Associations between the course of metabolic syndrome and levels of adiponectin, hs-CRP, IL-1Ra and IL-1β in males and females, adjusted for age, change in BMI, smoking status and physical activity (Mean ±95% CI)

6 Discussion

6.1 STUDY POPULATION, DESIGN AND METHODS

The study population consisted of five entire age groups (born in 1942, 1947, 1952, 1957 and 1962, n=1294) from one town. Three separate invitations were sent to subjects, according to the civil register, without any excluding criteria. The number of participants is representative (n=923, 71.3%, 411 men, 512 women) with no statistical gender differences in the number of subjects in any age group. Among the population of the second check-up, there were 681 same subjects as in the first check up (73.8%). Because this was a population-based study with invitations sent by mail, it is not possible to know the reasons why all of the invited persons did not participate or why some of them decided to participate only in one of the two check-ups. In previous research, among non-respondents there are those who have, in general, negative attitude towards medical care or who feel this kind of survey as an unpleasant reminder of own unhealthy lifestyle (308). The reason for non-respondence was not analyzed in this study but it, as well as the fact, that the study population is genetically homogenous, may limit the generalization of the results.

Two nurses, who interviewed and examined all the subjects, were specially trained for this task. At every stage, study subjects with elevated hs-CRP level (hs-CRP ≥ 10 pg/ml, except in Study IV hs-CRP≥ 30 pg/ml), were excluded; thus, latent infections or inflammatory conditions like tissue damage were unlikely to bias results as far as inflammatory markers are concerned. With these cut-off points of hs-CRP, bacterial and most viral infections are eliminated, according to previous research (309,310). The determinations of adiponectin and cytokines were done in the scientific laboratory of the University of Kuopio at the same time in 2003 in order to minimize inter-assay variations. The samples were immediately frozen to -20°C and stored in -70°C. Previous research shows evidence that adiponectin in samples stored in -70°C is reproducible, even after two frozen-thaw periods, with more years of storage than the samples in this research (311,312). Also, as regards inflammatory markers, storage in-70°C has been proven in previous research not to impair the reliability of the results (313).

The strengths of Study I are the population-based setting and moderately large number of subjects (403 men and 500 women). The fact that weight and height at the age of 20 years were asked instead of obtained from registers is a weakness. There is, however, support for that method in previous research, with the result that self-reported measurements can be used when estimating health risks, and that long-term memory of past weight is relatively good (314,315). Additionally, the retrospective setting with measurements of adiponectin and inflammatory markers only in middle age must be considered a limitation, as it only shows association with the change in BMI and not any prediction between these markers and BMI change. This setting does not, however, weaken the main findings concerning gender differences in this topic.

The percentage of smokers in Study II was 34% of males and 22% of females. This is in line with the statistics of the Finnish National Institute for Health and Welfare regarding

the number of smokers in Finland in 1996-1998 (316). In this study, diabetic subjects were also excluded; thus the associations of adiponectin and hs-CRP with smoking were examined in an apparently healthy population with a broad sampling of five age groups. However, the cross-sectional setting and the fact that other forms of tobacco were not examined must be considered as limitations.

In Study III, the number of subjects (both men and women) receiving medication for hypertension (n=40 vs. 40), diabetes (n=6 vs. 7) or hyperlipidemia (n=12 vs. 5) was relatively small and there were no gender differences in either medication group; thus, medications are not likely to bias the results. The MetS was observed in 35% of men and 34% of women, which is in line with earlier research (58, 59). However, the total number of subjects with the MetS was relatively small in this study (97 men and 93 women).

In Study IV, concerning the associations of inflammatory markers with the course of the MetS, the longitudinal setting is an advantage. However, the small number of subjects in the groups divided by the MetS status is a limitation. Additionally, there were only two health check-ups and points of laboratory measurements, which may bias the results; the status of the MetS may have varied according to the study period.

In addition to the limitations mentioned above, it is necessary to state that this study did not include accurate measurements of fat distribution; waist circumference was used instead. In epidemiological studies, this and other simple fat distribution measurements have proven to be useful and reliable, but naturally they cannot be as exact as measurements made using radiological methods (132). Another limitation is the fact that in this study, like in the majority of earlier population-based studies focused on inflammatory markers, only total adiponectin was determined instead of high-molecular-weight adiponectin or the ratio of high-molecular-weight and middle-molecular weight adiponectin, which seems to be especially related to insulin resistance (317).

6.2 ADIPONECTIN, IL-1RA AND HS-CRP ASSOCIATED WITH RELATIVE WEIGHT GAIN IN WOMEN

This study reveals that there is a gender difference in the association between the relative change in BMI from the age of twenty years to middle age and low-grade inflammation measured by adiponectin, IL-1Ra and hs-CRP, after adjusting for BMI in middle age. Adiponectin is associated linearly in an inverse fashion and IL-1Ra and hs-CRP are associated linearly with the change in BMI in women; there was no significant association in men.

Adiponectin levels are known to decline with weight gain, even before weight gain reaches the level of obesity (8). Furthermore, adiponectin levels have been shown to increase in subjects who manage to reduce their weight (318). On the other hand, the level of adiponectin at baseline was not found to be associated with future weight gain in Pima Indians. In another study of elderly subjects, adiponectin was not found to predict changes in weight (319,320). According to findings mentioned above, it might be presumed that decreased adiponectin may not perform an etiological role in obesity but more likely is a consequence of weight gain. There is evidence that adiponectin may act as a promoter in the network of inflammatory and anti-inflammatory cytokines. With decreased adiponectin synthesis, it is likely that the control mechanisms of the production of many inflammatory

and anti-inflammatory cytokines are inhibited (14). Not only is adiponectin capable of increasing the production of anti-inflammatory IL-1Ra, but it can also suppress the synthesis of several inflammatory cytokines and down-regulate CRP synthesis and secretion (14,24).

Physiologically, there is a gender-specific division in fat distribution: men have more visceral fat and women have more subcutaneous fat (321). Aging, in particular, increases the visceral fat component of weight gain in women (322,323). It has previously been suggested that the mass of intra-abdominal fat determines adiponectin levels (324). On the other hand, there is no evidence of gender difference in adiponectin levels when the amount of intra-abdominal and hepatic fat is similar between genders (325). In animal models, it has been shown that removal of visceral fat restores insulin action, elevates adiponectin levels and reduces inflammatory cytokine levels (326, 327). In the present study, adiponectin levels adjusted for BMI in middle age decreased significantly in a linear fashion with the relative change of BMI in women; this was not the case in men. The amount or distribution of fat was not examined in the present study. However, based on the research mentioned above, it can be presumed that with weight gain, fat accumulates primarily in the intra-abdominal division and is relatively more abundant in elderly women than in men (322, 323). This presumption might partly explain the finding of this study concerning a gender-specific difference in adiponectin levels.

White adipose tissue is the main producer of IL-1Ra in obesity and inflammation, and it is speculated that this cytokine contributes to future weight gain (20). There is evidence that IL-1Ra may be differentially secreted and may also function differently in men and women (37). In another study carried out in subjects with Cushing syndrome, elevated IL-1Ra levels were particularly associated with centrally-located fat (328). In women, weight gain and particularly increased accumulation of central body fat begin before menopause (323). In the present study, after adjusting for BMI in middle age, IL-1Ra was associated with relative weight change only among women. The present results concerning this gender difference in IL-1Ra levels, while not capable of revealing any causality between IL-1Ra and increased BMI could stem from the earlier results mentioned above. The present findings concerning the decrease in adiponectin levels and the increase in IL-1Ra levels in women are also in line with previous results (37, 322, 323) concerning the relationship between adiponectin and IL-1Ra, and they may give further support to the theory that adiponectin acts as a promoter in the network of inflammation.

In this study, no association between IL-1β and relative change in BMI was found. This might be due to the previously known fact that IL-1β levels are often not elevated in circulation (16). Furthermore, increased IL-1β levels are speculated to be associated with pancreatic β-cell damage and the diabetic state (329). In the present study population, there were only a few diabetic subjects.

It has been previously confirmed that weight gain and obesity influence the development of the MetS and T2D through inflammatory mechanisms (14). In a study of the associations between components of the MetS and CRP, the strongest association was found between CRP and BMI; furthermore, CRP levels increased with an increasing number of components of the MetS (213). In the present study, hs-CRP was significantly and positively associated with the relative change in BMI in both genders. After adjusting for BMI in middle age, this association disappeared in men and remained significant in

women. This result is in line with a study on the effect of weight gain on pulmonary diseases and systemic inflammation measured by hs-CRP, in which weight gain had a stronger effect on inflammation in women than in men (330). That kind of gender difference was also presented in a follow-up study of 11 years, concerning change of body composition and inflammatory markers (331).

It is well known that lower socio-economical status is firmly linked to greater weight gain in Western countries (332,333). In the present study, duration of education was used as a marker of socio-economical status. A gender difference was also found in this respect, with a greater relative change in BMI in women with lower education level. The MetS has been observed to have a different association with the risk of CVD between genders; it is a stronger predictor of cardiovascular diseases in women than in men and has a greater effect on left ventricular function and hypertrophy in women, compared to men (32,33). Based on these results, we should pay special attention to the health counseling of young women with lower education levels (which may reflect lower socio-economical status) in order to prevent cardiovascular consequences.

The findings of this study concerning the associations between relative weight change and decreased adiponectin levels and increased IL-1Ra and hs-CRP levels in women but not in men support the theory that the underlying mechanisms of obesity and obesity-related diseases differ between genders. It can be concluded that an increase in fat mass may be more harmful to women than men with respect to adiponectin and inflammatory markers. However, further research with a prospective study setting is needed to confirm these results.

6.3 SMOKING, HS-CRP AND ADIPONECTIN

The novel finding in this study was the gender difference in levels of adiponectin and hs-CRP related to smoking in a non-diabetic population; in males, hs-CRP, but not adiponectin, was associated with smoking; in females, there was an association between adiponectin and smoking, but not between hs-CRP and smoking.

Earlier research reveals a significant inverse association between adiponectin and smoking in both genders (181). In another study with smoking males, a significant decrease of adiponectin levels was seen in currently smoking men, compared to men who never smoked (277). The association was still present when diabetic subjects and subjects with regular drug use were excluded, but what is noticeable is that these men were likely ten years older in terms of mean age compared to smoking men in the present study, which may affect to the results. Similar with the results of the present study, Sonmez et al. did not find in their work any alteration in adiponectin levels in the population of healthy young male smokers with regular exercise habits, compared to non-smokers (334).

The associations between smoking and adiponectin levels in women have been hardly studied. Smoking has been speculated to directly affect fat distribution via an increase in visceral fat deposits (335). This theory is supported by the results where especially in premenopausal women smoking was associated with increased visceral fat and reduced femoral fat, compared to non-smoking women (336).

The present study found an association between elevated hs-CRP in male smokers compared to non-smoking males; this is in line with earlier results (337, 338). Additionally

there is evidence in the COPD study that higher CRP levels are associated with a higher decline in FEV1 in men, compared to women (339). Unlike other previous studies which also included diabetic subjects, hs-CRP levels were not associated with smoking in the non-diabetic female population of this study (340). Contrary to synthesis of adiponectin, which appears mainly in adipocytes of subcutaneous adipose tissue, inflammatory cytokines are secreted mostly from non-fat cells in adipose tissue (341). Smoking might have an influence on compounds of visceral adipose tissue outside the adipocytes, causing the release of interleukin-6, which results in increased hs-CRP production in hepatic cells (342). Due to the larger visceral fat deposits present in men, there may be greater production of hs-CRP in men compared to women, as seen in the present study.

In conclusion, there was a gender difference in the associations between smoking and adiponectin and hs-CRP levels found in the present study. This finding may suggest that the detrimental effects of smoking may be partly mediated by different paths, according to gender. Further research is warranted to determine whether fat distribution can explain gender-specific associations of adiponectin and hs-CRP with smoking. Both adiponectin and hs-CRP are indicators of future risk of the MetS and CVD. The results of this study thus further support harmful effects of smoking.

6.4 GENDER DIFFERENCES REGARDING LOW-GRADE INFLAMMATION IN SUBJECTS WITH ELEVATED BLOOD PRESSURE AND THE METABOLIC SYNDROME

In Study III, it was shown that in hypertensive subjects with the MetS, as defined by NCEP criteria, women had higher levels of IL-1Ra and hs-CRP compared to men. Furthermore, absolute differences between genders in these inflammatory markers were greater in subjects with the MetS, compared to subjects without the MetS. Additionally, women had a threefold risk for the MetS in the lowest adiponectin tertile, compared to the highest one, even after removal of potential confounding factors, while no statistical OR for the MetS was found in men. Though adiponectin levels were higher in women despite their MetS status, the absolute difference between genders was about 1.3 μg/ml lower in the subjects with the MetS compared to subjects without the MetS. This suggests that adiponectin is a more important factor in the MetS in women, compared to the MetS in men, at least in hypertensive subjects. In women, fat is known to accumulate in the subcutaneous depots, especially in the gluteal-femoral region (343). With the MetS, accumulation of visceral fat also increases in women (344). This change in fat deposits may lead to a decrease in adiponectin production. While an adiponectin decrease has been assumed to lead to dysregulation of those control mechanisms that inhibit the production of pro-inflammatory cytokines (14), it can be speculated that a greater decrease in adiponectin levels in women (compared to men) reflects more severe low-grade inflammation in women than in men with the MetS.

IL-1β is shown to be increased in visceral adipose tissue in obese subjects and also in patients with essential hypertension, but IL-1β levels are seldom elevated in plasma, while anti-inflammatory IL-1Ra is constantly present in the circulation and antagonizes IL-1β binding to the cell receptors (16, 20). Increased IL-1β levels are often associated with elevated levels of hs-CRP, which is synthesized in the liver in response to IL-1β (345).

Previously there has been evidence that elevated IL-1Ra levels might be associated with centrally located fat (328).

A statistically significant gender difference in the ratio of hs-CRP levels between subjects with and without the MetS was detected in the present study, indicating that the absolute increase in hs-CRP was greater in women, compared to men, among subjects with the MetS. Furthermore, there was a larger relative increase in IL-1Ra levels in women with the MetS than in men with the MetS. These findings might also be explained by altered fat distribution, with more centrally located fat as mentioned earlier in this text. These findings are also in line with previous results that disturbances in the regulation of inflammatory cytokines are associated with decreased adiponectin levels (14).Regarding gender-specific associations of CRP with insulin resistant states, the earlier results are controversial. High levels of hs-CRP proved a better predictor of type 2 diabetes in women than in men in the MONICA/KORA study (34). Increased CRP levels were also more pronouncedly related to the components of the MetS in women than in men in a Japanese study with an apparently healthy population (346). On the other hand, in the Hoorn study a significant association of hs-CRP with incident diabetes mellitus was observed in men, but not in women (347). In Japanese subjects, this association was observed in both sexes (348); in the Mexico City Diabetes Study it was only observed in women (294).

Elevated plasma insulin is widely used as a marker of insulin resistance (349), at least in large population studies where more accurate methods such as the insulin clamp technique cannot be used. Excessive mobilization of free fatty acids takes place in the visceral adipose tissue through a higher rate of lipolysis in visceral fat, compared to subcutaneous fat. High levels of free fatty acids inhibit insulin-mediated glucose uptake in skeletal muscle, leading to insulin resistance (87,350). The increase in circulating free fatty acids also increases insulin secretion, leading to hyperinsulinemia. In the present study, insulin resistance measured by fasting insulin was similarly associated with the MetS in both genders, showing a risk of the MetS to be 22-fold in men and 18-fold in women in the highest tertile of fasting insulin, compared to the lowest tertile. This risk remained statistically significant even after adjustment for BMI, emphasizing the central role of insulin resistance in the MetS.

In conclusion, in hypertensive subjects gender differences were found in relation to adiponectin, hs-CRP and IL-1Ra and the MetS. Low-grade inflammatory markers were more pronouncedly present and the changes in their levels were more disadvantageous in women than in men. Further research is needed to estimate the significance of these findings and possible connections to the previously shown results that the MetS may be a stronger predictor of cardiovascular diseases among women, compared to men (32).

6.5 ADIPONECTIN AND INFLAMMATORY MARKERS IN THE COURSE OF THE METABOLIC SYNDROME

The novel finding in this longitudinal follow-up study of 6.5 years was the baseline adiponectin, and also IL-1Ra and IL-1β levels, to predict the Incident MetS. Additionally, this data suggested that higher adiponectin levels and lower hs-CRP and IL-1Ra levels may predict the resolution of the MetS.

The MetS is strongly associated with obesity. The change in BMI has been shown to predict the development of the MetS in several studies (351 - 354), which has led to speculations that the change in BMI is the central factor in the course of the MetS. In the present study, adiponectin was found to predict the course of the MetS independently of the change of the BMI. Adiponectin levels are associated inversely with obesity, the MetS and inflammatory markers (14,166). Low adiponectin levels have also been considered as an independent risk factor for the MetS (355). On the other hand, there is evidence in a study carried out with the Pima Indian population that high adiponectin levels provide protection against T2D (173). The findings in the present study concerning the association of higher baseline adiponectin levels with a more favorable course of the MetS are in line with these earlier findings and provide further support to the theory that adiponectin may partly modulate the process underlying the development of the MetS.

IL-1Ra is known to possess anti-inflammatory properties, but it also reflects the inflammatory response (16). Both IL-1Ra and IL-1β levels have been found to increase in the MetS, and it has been suggested that they may be better markers of the MetS than TNF-α or interleukin-6 (161). Increased IL-1Ra levels are known to precede T2D (194). After the present results were collected, another Finnish study has come out in which it was shown that IL-1Ra predicts the MetS to proceed to incident diabetes independently of CRP or traditional risk factors (356); however, in a literature review, no research was found concerning IL-1Ra as a predictor of the MetS. In a study of increased IL-1Ra preceding T2D, the investigators speculated that IL-1Ra may protect against the pro-inflammatory effects of IL-1β, or, on the other hand, have independent metabolic effects leading to insulin resistance. It was not possible to find further information concerning that speculation, but nevertheless these earlier findings support the results of the present study in terms of the association between elevated IL-1Ra levels and both Incident and Persistent MetS, which often precede type 2 diabetes. The results of this study are also in line with recent findings in which subjects with an intense pro-inflammatory state measured also by IL- 1Ra, regardless of BMI, have a higher probability of developing the MetS (195).

In this study, it was found out that lower IL-1β levels are associated with Incident MetS in males and in the combined study population, which is a somewhat surprising result when previous data is taken into account. Compared to other cytokines, it seems that the synthesis and secretion of IL-1β is more strictly regulated (357). Furthermore, IL-1β has also been speculated to be associated with pancreatic β-cell damage and a diabetic state (329). A low IL-1Ra/IL-1β ratio is associated with newly diagnosed insulin-dependent diabetes mellitus and with certain inflammatory states like osteoarthritis (197,198). The present population included only a few diabetic subjects, which may also have affected the IL-1β levels measured in this study.

CRP synthesis is decreased by adiponectin and it is stimulated by IL-1β and IL-6 (24,358,359). Those subjects in the present population who had the MetS at both check-ups had higher absolute hs-CRP levels, which might indicate longer and more advanced low-grade inflammation, compared to the other three groups. Longer exposure to low-grade inflammation in the Persistent MetS group might partly explain the finding that there was no significant association between hs-CRP and Incident MetS, but that such an association was observed when Persistent and Resolute groups were compared. In the present study, however, the exact length of the different MetS statuses was not examined, so this can only

be speculated about. This speculation, however, is supported by earlier research, which provides evidence of hs-CRP acting as a marker of vascular inflammation instead of directly promoting atherosclerosis (359).

In conclusion, decreased adiponectin level and increased levels of hs-CRP and IL-1Ra were found in this study to associate with the persistence of the MetS. These findings provide further support to the role of inflammation in the MetS. Further research is warranted to determine whether adiponectin or other inflammatory markers could be used in clinical practice when trying to predict the course of the MetS and risk of CVD and T2D.

7 Summary and Conclusions

This study was done to evaluate adiponectin and low-grade inflammatory markers with factors that generally precede the MetS. Additionally it was aimed at investigating levels of low-grade inflammatory markers with respect to the course of the MetS. Due to evidence presented in earlier research, a gender-specific view was adopted in this study.

The main results were:

1. Decreased adiponectin and increased hs-CRP and IL-1Ra levels were associated with a relative increase in BMI from twenty years to middle age in women, but not in men. The proportion of women with lower socioeconomic status and education increased with relative weight gain; in men there was no such association.
2. In an apparently healthy non-diabetic population, increased hs-CRP levels in men and decreased adiponectin levels in women were associated with smoking.
3. Women with elevated blood pressure and the MetS had significantly higher levels of IL-1Ra and hs-CRP, compared to men. In insulin levels no gender differences were seen. In hypertensive women with the lowest tertile of adiponectin, the risk for the MetS was threefold; no association was seen in men.
4. Decreased baseline adiponectin and increased IL-1Ra levels were associated with the appearance and the persistence of the MetS. Increased baseline hs-CRP was associated with the persistence of the MetS. No gender differences were seen in the association between adiponectin, low-grade inflammation and the course of the MetS in this study population.

In conclusion, decreased adiponectin levels in women were associated with grater relative weight gain, smoking and, especially, in the hypertensive women with an increased risk for the MetS. Grater relative weight gain was associated with increased inflammatory markers in women, but this association was not seen in men. Women with elevated blood pressure and the MetS had increased low-grade inflammatory markers compared to men. Hypoadiponectinemia and increased low-grade inflammation suggest an unfavorable course of the MetS in both genders.

8 Future directions

This study adds to the growing evidence that low-grade inflammation is associated with metabolic risk factors like weight gain, smoking and hypertension. Gender differences found in the results suggest that low-grade inflammation may be mediated differently between sexes. The inflammatory markers may be beneficial in terms of the detection of the MetS and its progression to CVD and/or T2D.

From the present data it is not possible to draw any causal relationship between low-grade inflammation and the progression of the MetS. In the future, it will be important to also characterize other inflammatory mediators. A continuous chain from epidemiologic observation to biochemical background and treatment intervention is warranted. Some preliminary treatment interventions have already been done that suggest the role of inflammation in the progression of T2D. Promising results have been published on the ability of anakindra, specific IL-1Ra antibodies, to slow down the clinical progression of T2D (360).

It is imperative for clinical medicine to find a simple and affordable test to reliably detect the MetS and its risk to progress to diabetes and/or premature cardiovascular morbidity, in order to be able to focus on better prevention and treatment for high- risk individuals.

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Tiina Maarit Ahonen

Adiponectin and Low-Grade Inflammation in Relation to Preceding Factors and the Course of the Metabolic Syndrome

A Gender-Specific View

Inflammation, which is associated with the metabolic syndrome, was examined in relation to preceding factors of this syndrome. The results show that, from the aspect of inflammation, an increase in relative weight is more harmful to women than to men. Females who smoke may be more prone to development of inflammatory state due to lower adiponectin levels, compared to males. Increased low-grade inflammation at baseline may refer to an unfavorable course of the metabolic syndrome in both genders.

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