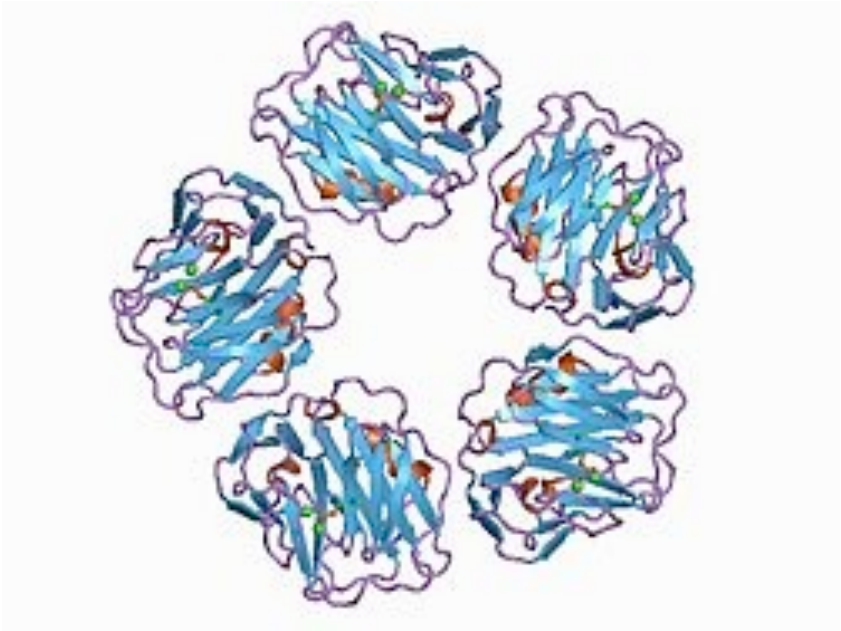
High sensitivity C-reactive protein - a useful tool in risk assessment of patients with abdominal obesity?



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Abstract

Background: Many obese will eventually develop diabetes and cardiovascular disease. The metabolic syndrome is a cluster of risk factor for these diseases, and low-grade inflammation has been linked to all three conditions.

Thesis aims: To investigate if high-sensitivity C-reactive protein can be a useful tool in risk assessment for the development of the metabolic syndrome in abdominally obese patients. Also, to explore what recent studies have found regarding the significance of the abdominal adipose tissue is in this syndrome.

Material and method: The thesis is a litterature study. The medical database PubMed was used to search for relevant articles.

Results & conclusion: Increasing waist circumference is independently associated with hs-CRP, indicating that abdominal obesity is associated with low-grade inflammation. Hs-CRP correlates with individual factors in the metabolic syndrome, but it does not seem to add any information to the formal criteria. It can not predict the presence of the metabolic syndrome.

Content

Abstract.....1

Content.....2

1.0 Introduction & thesis central question.....4

2.0 Method.....6

3.0 Results.....7

3.1 Basic concepts.....7

3.1.1 C-reactive protein - a short introdution.....7

3.1.2 Common disorders of glucose metabolism related to obesity.....7

3.1.3 An overview of cardiovascular disease (CVD).....8

3.2 Low-grade inflammation & inflammatory mediators.....9

3.2.1 C-reactive protein - an acute phase reactant.....9

3.2.2 Low-grade inflammation and metabolic stress.....10

3.2.3 C-reactive protein - its characteristics and current uses in clinical practice and research.....10

3.2.4 Obesity and adipose tissue-derived inflammatory mediators.....12

3.2.5 Adipokine levels in adipose tissue dysfunction.....13

3.2.6 Adipose tissue-induced production of CRP.....14

3.3 The metabolic syndrome - a risk factor cluster.....15

3.3.1 Confusing definitions and guidelines.....15

3.3.2 The relationship between hs-CRP and the individual components of the metabolic syndrome.....17

3.3.3 Can hs-CRP predict the presence of the metabolic syndrome?.....19

4.0 Discussion.....21
4.1 Is adipose tissue dysregulation the key to low-grade inflammation in abdominal obesity?.....21
4.2 Hs-CRP - does it add information beyond the metabolic syndrome criteria?.....21
5.0 Conclusions.....23
Bibliography.....24

1.0 Introduction & thesis central question

There is an obesity pandemic among us which the health care systems are not ready for. The World Health Organization estimates that nearly 1,5 billion adults worldwide are overweight (BMI ≥ 25), and of those 500 million people are clinically obese (BMI ≥ 30). Overweight and obesity are now the 5th leading risk for global deaths [1]. Many clinically obese will eventually develop diabetes and most of them will die of cardiovascular disease, the number one cause of death globally [2].

The four conventional cardiovascular risk factors are still smoking, diabetes/obesity, hypertension and hypercholesterolemia, but the abscence of these does not fully protect from the development of cardiovascular disease. At least 10-20% of cardiovascular events occur in individuals without traditional risk factors [3], and many patients with cardiovascular events have cholesterol levels below standard interventional thresholds [4]. This has raised the question of whether or not new tools are needed in cardiovascular risk assessment.

Hs-CRP is the most extensively studied inflammatory biomarker in cardiovascular disease. In the last 10-15 years it has emerged as a promising indicator of cardiovascular disease risk idependent of other risk factors. The metabolic syndrome is a clustering of risk factors for diabetes and cardiovascular disease, and abdominal obesity is a central feature in this syndrome. The syndrome is recognized as both a proinflammatory and prothrombotic state, but the cause of this is not yet fully understood [41] [42, 43]. I wanted to know if hs-CRP could be used in risk assessment at an early stage, when type 2 diabetes and cardiovascular disease has not been established. If so, the test could be a tool in the prevention of morbidity and mortality associated with these diseases.

The central question of this thesis is:

«Can high-sensitivity C-reactive protein be a useful tool in risk assessment for the development of the metabolic syndrome, and what is the significance of the abdominal adipose tissue in this syndrome?»

This is a thesis of limited size, and the field of adipose tissue pathophysiology is vast and ever-expanding. I have chosen to focus on the inflammatory aspect of the abdominal adipose tissue in the metabolic syndrome, i.e. its production of cytokines, and the relationship to C-reactive protein production.

2.0 Method

This thesis is a litterature study in which I have used the medical database PubMed to search for relevant articles. I used the following key words alone or in combinations to search for information on topics of interest:

inflammation, CRP, C-reactive protein, high-sensitivity C-reactive protein, hs-CRP, cytokines, adiopokines, atherosclerosis, cardiovascular disease, CVD, type 2 diabetes, insulin resistance, obesity, abdominal obesity, central obesity, metabolic syndrome, risk, prognostic.

I also used other sources of information for background research, such as internationally acclaimed textbooks and websites like uptodate.com and Norsk Elektronisk Legehåndbok (legehandboka.no), all known for researched based information for clinicians.

There are several definitions of the metabolic syndrome. This has created confusion among clinicans and researchers, making it difficult to directly compare data from studies where different definitions has been used. However, the definitions are quite similar so in this paper I have chosen to compare papers regardless of which definition has been used, as long as waist circumference/ abdominal obesity was one of the factors studied. I have also chosen to use studies where BMI was one of the criteria where this was appropriate. I also use central obesity, abdominal obesity and increased waist circumference interchangeably, as does most definitions of the metabolic syndrome.

3.0 Results

3.1 Basic concepts

3.1.1 C-reactive protein - a short introduction

C-reactive protein is a well-known unspecific marker of inflammation and tissue damage. Is is part of a family of molecules called acute phase reactants made by the liver cells. The role of CRP is not fully understood, but we know that it plays a role in host defence and in clearance of apoptotic and necrotic cells. Common analysis indications in clinical use today are suspected bacterial infections, differentiating between viral and bacterial infections, following disease processes and detecting postoperative complications **[5]**.

3.1.2 Common disorders of glucose metabolism related to obesity

Insulin resistance is a state where a subnormal glucose response is seen for a given concentration of insulin. The central feature is hyperglycemia, i.e when insulin becomes less effective at lowering blood glucose levels. However, insulin have several other functions and the effects depend on the cells involved. The most important tissues affected by insulin resistance are muscle, fat and liver. As an example, in an insulin resistent patient the adipocytes may reduce their uptake of circulating lipids and increase mobilization of stored lipids, resulting in elevated triglyceride levels in the blood **[6]**.

When risk factors for type 2 diabetes are clustered with risk factors for cardiovascular disease, we call it the **metabolic syndrome**, also called insulin resistance syndrome or syndrome X **[7] [8]**. The details of the metabolic syndrome will be further discussed in the next section of this thesis.

Type 2 diabetes is a metabolic disease characterised by chronic hyperglycemia with varying degrees of insulin resistance and/or relative insulin deficiency. 90% of patients with diabetes have type 2 diabetes and many are unaware that they have the disease. Several studies have demonstrated a strong association between both insulin resistance & the metabolic syndrome and risk for development of type 2 diabetes **[9] [10] [11] [12]**. The most important risk factors for type 2 diabetes are obesity (particularly abdominal/central obesity) and physical inactivity **[13]**. The long term effects of type 2 diabetes are the same as for type 1 diabetes: Micro- and macrovascular disease, neuropathy and nephropathy. The overall risk of dying is doubled in patients with diabetes compared to non-diabetics **[14]**. Studies has also shown that the relative risk for fatal coronary heart disease in women with type 2 diabetes is 50% higher then in men with the disease **[15]**. 3,2 million people die each year from complications associated with diabetes. 75-80% of them die of cardiovascular disease **[13, 14]**.

3.1.3 An overview of cardiovascular disease (CVD)

Cardiovascular disease is defined as disease relating to or of the heart and blood vessels. The pathological process of atherosclerosis is responsible for most cases of cardiovascular disease. There are four major areas of cardiovascular disease seen from a diagnostic standpoint **[16]**:

* Coronary heart disease (angina pectoris, myocardial infarction, heart failure and coronary death). Accounts for about 1/3-1/2 of the total cases of CVD.
* Cerebrovascular disease (stroke and transient ischemic attack)
* Peripheral artery disease (intermittent claudication)
* Aortic atherosclerosis & thoracic and abdominal aneurisms

Hypertension and dyslipidemia are well established risk factors, as is diabetes. Lifestyle factors like smoking, obesity, diet and exercise can also have a great impact on cardiovascular disease risk **[16]**.

3.2 Low-grade inflammation & inflammatory mediators

3.2.1 C-reactive protein - an acute phase reactant

Inflammation is a protective mechanism which organisms depend upon for survival. Without it damaged tissue can not heal and infections can not be fought. It is not a disease, but a non-specific response that is beneficial to the organism.
Inflammation and tissue injury is followed by the acute phase respons, a group of physioloigcal processes that occur soon after the onset of trauma, infection, inflammatory processes and other non-physiological states. The acute phase response comprises several factors like fever and increased vascular permeability. It also includes a change in the concentration of acute phase reactants in the serum.

C-reactive protein is an well-known unspecific marker of inflammation and tissue damage, although its functions has not yet been fully established. Its rapid response shows that it is a part of the innate immune system. It is one of many known acute phase reactants produced by the hepatocytes.
Acute phase reactants are proteins whose serum concentrations increase or decrease at lest 25% during inflammatory states. Changes in the levels of these proteins are influenced by inflammatory molecules called cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha). During inflammatory processes cytokines are mainly produced by immune cells like

monocytes and macrophages, but can also be produced by other cells, such at fat cells. Despite being called acute phase reactants they not only accompany acute inflammatory conditions, but also chronic inflammatory states **[17]**.

3.2.2 Low-grade inflammation and metabolic stress

Inflammation and its significant role in chronic diseases has been extensively researched and is becoming widely accepted. In February 2004, it was featured as the cover story in the popular magazine *Time*, named «The Secret Killer». Chronic low-grade inflammation has been shown to play a key role in cardiovascular disease; throughout the atherosclerotic process from endothelial dysfunction to plaque rupture and thrombosis. The state of low-grade inflammation, also called para-inflammation or subclinical inflammation is, unfortunately, not very well defined. The signs of acute inflammation are missing here and the acute-phase response is only minor. It seems that the purpose of low-grade inflammation is to restore homeostasis in times of metabolic stress, and not to fight infection or clear necrotic cells as is the case with acute inflammation. This appears to be the basis for low-grade inflammation as seen in obesity, diabetes and cardiovascular disease **[18] [19]**.

3.2.3 C-reactive protein - its characteristics and current uses in clinical practice and research

C-reactive protein is an acute phase protein of the pentraxin family, shaped as an annular pentameric disc. It was discovered in the 1930s and got its name from its ability to bind to the C-polysaccharide in the capsule of the pneumococcus bacteria [20]. It is synthesized in the liver by hepatocytes in response to inflammatory

processes. It is up-regulated by cytokines, interleukin-6 being the chief stimulator of CRP production [21]. In healthy individuals the levels of CRP are seldom above 5 mg/L, with medians values ranging from 0,9 mg/L - 2,05 mg/L in different studies [5, 22]. High plasma concentrations are seen 6-12 hours after the initiation of a disease process, and it may increase several hundred-fold. It has a half-life of 15-25 hours, so its concentration falls fast as the healing progresses. Higher values are seen in diseases characterized by cell necrosis, and values above 40 mg/L may suggest bacterial infection [5]. It is a stable molecule and can easily be measured at any physicians office with a simple blood test. In general practice C-reactive protein is commonly used to differentiate between bacterial and viral infection, but also to follow disease progression. In addition, in hospital settings it is often used to detect postoperative complications [5].

With new and improved antibodies available it is possible to measure concentrations of CRP with greater accuracy, specifically in the lower range. This analysis is called high-sensitivity CRP or micro-CRP, and is a sensitive marker for low-grade inflammation. It can measure serum concentrations down to 0,05-0,1 mg/L. It has been used in research for at least 10-15 years, but is not in common clinical use as of today. In 2003 the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) recommended patient stratification into three groups in cardiovascular disease risk assessment: low risk (hs-CRP< 1mg/L), intermediate risk (hs-CRP 1-3 mg/L) and high risk (hs-CRP> 3 g/L) [23]. They concluded that hs-CRP was the analyte of choice to identify patients for primary prevention of cardiovascular disease. They did not recommend widespread use of hs-CRP for screening for cardiovascular disease risk. Moderate level of evidence (level C) resulted in the test being labeled «optional». They found that hs-CRP measurements appeared to be best employed to detect cardiovascular disease risk in patients with intermediate risk, i.e. with 10-20% risk of coronary heart disease over 10 years. These are patients without known CVD

but who may be at higher absolute risk than estimated by major risk factors. The reaserch group concluded that hs-CRP could be used to adjust risk for CVD in these patients [23].

As a result, traditional cardiovascular disease risk score algorithms like the Framingham Risk Score are now being challenged by new risk-prediction models that incorporate hs-CRP. The Reynolds Risk Score is one such model [57]. In addition to the traditional risk factors it also includes hs-CRP and genetic risk. Studies have shown that it improves risk classification and the accuracy for total risk prediction, particularly for those classified as intermediate risk by usual algorithms [58] [59] [60].

Since CRP is an unspecific inflammatory marker, single measurements can be hard to interpret. As a result, a low level has more predictive value than a high one. A slight increase in CRP concentration needs to be confirmed by new blood samples. Several measurements should be taken in these cases, preferably at least three weeks apart, in order to be able to interpret the results and assess cardiovascular disease risk [5] [24].

Hs-CRP has been shown to predict the development of type 2 diabetes and cardiovascular disease independently of established risk factors, and these studies has added to the growing body of evidence of low grade inflammation in the pathogenesis of type 2 diabetes and cardiovascular disease [25] [4] [26] [37].

3.2.4 Obesity and adipose tissue-derived inflammatory mediators

The World Health Organization estimates that nearly 1,5 billion adults worldwide are overweight (BMI ≥ 25), and of those 500 million people are clinically obese (BMI ≥ 30). Overweight and obesity are now the

5th leading risk for global deaths **[1]**. The close relationship between abdominal obesity, metabolic disturbances and cardiovascular disease has been apparent for clinicians throughout the ages. We now know that adipose tissue is not just a storage facility for fatty acids. It is an active endocrine organ, producing bioactive proteins named adipokines (or adipocytokines - adipose tissue-derived cytokines) **[27, 28]**.

One of the most widely known is the hormone leptin (from the greek *leptos*, meaning thin), which was discovered in the mid 1990´s. It is almost exclusively secretet by adipocytes. It is a signal that reduces appetite, and for that reason it became the subject of intense research as many hoped it held the key to a cure for obesity **[29]**. The level of leptin circulating in the body is directly proportional to the total amount of body fat. As a result obese people have high levels of leptin.

Other adipokines include interleukin-6, adiponectin, resistin, adipsin, tumor necrosis factor-alpha, plasminogen activator-inhibitor-1 and many more. This is a relatively new area of research, so there may be more discovered in the years to come. Also, some of the adipokines are produced by other cells as well as by adipocytes. The adipokines are involved in a multitude of processes like inflammation, insulin resistance, lipid metabolism, blood pressure, macrophage infiltration, fibrinolysis, food intake, fat mass regulation and more **[30]**.

3.2.5 Adipokine levels in adipose tissue dysfunction

Obesity and adipose tissue has been shown to be associated with low-grade inflammation **[31]**, and it is also strongly associated with inflammation and increased CRP-levels in obese, but healthy, people or people with subclinical disease **[32][33]**. The levels of plasma adipokines rise as adipose tissue/adipocytes increases in volume,

except for adiponectin which decreases (reduced synthesis of adiponectin is seen in obesity, insulin resistance, metabolic syndrome and type 2 diabetes **[34] [35]**). There seems to be a shift toward proinflammatory adipokine dominance as adipcytes become enlarged **[36]**. In other words, there is an up-regulation/ hypersecretion of pro-inflammatory adipokines, and a decreased production adiponectin (an anti-inflammatory adipokine only produced in adipose tissue) **[30]** when fat tissue expands. The explanation for this has been suggested to be that as adipocytes becomes hypertophic, hypoxia may occur (due to hypoperfusion) inducing cellular stress **[37]**. This stimulates the expression of inflammatory genes and activates immune cells. There is an increase in macrophage infiltration in the increasing adipose tissues **[38] [39]**, and both macrophages and adipocytes secrete cytokines.

3.2.6 Adipose tissue-induced production of CRP

Two of the first cytokines/adipokines to be associated with low-grade inflammation were interleukin-6 and tumor necrosis factor-alpha, and these have been shown to be up-regulated in obese patients **[28]**. Studies has shown that levels of CRP are significantly related to levels of IL-6 and TNF-apha **[40]**. Interleukin-6 is, as mentioned earlier, the chief stimulator of CRP production. Abdominal adipose tissue, with its increased production of cytokines from both immune cells and adipocytes, is drained directly to the portal circulation. It could be that this direct route to the liver, where CRP is produced, is partly responsible for the increased production of CRP in abdominally obese people **[30]**. Weight loss has shown to significantly decrease CRP levels in obese subjects **[41][42]**, which could support the theory that the adipose tissue is actively involved in the low-grade inflammatory state seen in abdominally obese people.

3.3 The metabolic syndrome - a risk factor cluster

3.3.1 Confusing definitions and guidelines

As mentioned earlier, the metabolic syndrome is a cluster of many important and established risk factors for cardiovascular disease and type 2 diabetes. The concept later defined as the metabolic syndrome was first suggested by Reaven in 1988 **[43]**, and several different definitions have been in use since it was first defined by WHO in 1998. Many are still in use, as there is no universal definition. There has also been much debate in the medical establishment about this fact and of whether or not it is a real syndrome **[44]**. Following are some of the most widely used definitions:

The International Diabetes Federation definition, updated in 2005/2006, states that:

«*... for a person to be defined as having the metabolic syndrome they must have:*

Central obesity (defined as waist circumference ≥ 94cm for Europid men and ≥ 80cm for Europid women, with ethnicity specific values for other groups). If BMI is > 30, central obesity can be assumed and waist circumference does not need to be measured.

plus any two of the following four factors:

** Raised TG level: ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality*

** Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L*) in males and < 50 mg/dL (1.29 mmol/L*) in females, or specific treatment for this lipid abnormality*

** Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension*

** Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes*
If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome. » [45]

The IDF concensus group of 2006 highlighted several parameters they thought should be included in research studies to «help determine the predictive powers of these extra criteria for CVD and/or diabetes.» Among the areas mentioned for further study was the proinflammatory state - with elevated hs-CRP, elevated inflammatory cytokines (eg TNF-alpha and IL-6) and decreased adiponectin plasma levels. The prothrombotic state was another important area for further study according to the group **[45]**.

In 2009, several major organizations, like the International Diabetes Federation and the American Heart Association, met in an attempt to unify the many different criteria used **[44]**. The resulting statement gave us new criteria for the metabolic syndrome with no obligatory components, and three out of five abnormal criteria qualify for the syndrome. The diagnostic criteria in this definition are:

* Elevated waist circumference: Poulation- and country-specific definitions
* Elevated triglycerides: ≥ 150 mg/dL (1.7 mmol/L). Drug treatment for elevated triglycerides is another indicator.
* Reduced HDL-C: < 40 mg/dL (1.0 mmol/L) in males; < 50 mg/dL (1.3 mmol/L) in females. Drug treatment for reduced HDL-C is an alternate indicator.
* Elevated blodd pressure: Systolic ≥ 130 mm Hg and/pr diastolic ≥ 85 mm Hg. Antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator.

* Elevated fasting blood glucose: ≥ 100 mg/dL. Drug treatment of elevated glucose is an alternate indicator. (Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria) **[44]**.

The group ended their statement by saying: «... further studies exploring the relation of waist circumference thresholds to metabolic risk and cardiovascular outcomes in different populations are encouraged, and we continue to recommend the use of waist measurement as a useful screening tool in many primary care situations.»

Although the International Diabetes Federation was part of the 2009 statement above, they still use their own definition from 2006 on their web page and in their publications **[46]**. This illustrates that there is still no universal definition. However, the when two commonly used criteria were compared, the definitions overlapped in 93% of of the subjects in determining the presence or absence of the syndrome **[47]**.

3.3.2 The relationship between hs-CRP and the components of the metabolic syndrome

Increased levels of CRP has been found in obese people, and patients with metabolic syndrome have been found to have what the authors judged to be high-risk levels **[48] [49]**. Also, increasing number of components correlates with increasing CRP-levels **[50] [48]**. As the metabolic syndrome has several components, it could be that hs-CRP elevation is related to just one or some of these components. Several studies have been done to investigate the relationships between hs-CRP and the different components of the metabolic syndrome.

A cross sectional study on nondiabetic subjects done by Yudkin et al. showed that levels of CRP were related to all measures of obesity. CRP-levels were also related to insulin resistance, blood pressure, HDL, and triglycerides and markers of endothelial dysfunction. The authors concluded that these research data suggested that adipose tissue is an important determinant of low-grade chronic inflammation, and that chronic low-grade inflammation may induce insulin resistance and endothelial dysfuction. They also stated that this could be a possible link between insulin resistance and endothelial dysfunction and obesity & cardiovascular disease **[40]**.

A Tunisian case control study concluded that waist circumference was an significant independent predictor of elevated CRP levels in both men and women with the metablic syndrome **[51]**. Also, HDL-C was another significant predictor of elevated CRP levels in women only.

A cross sectional study from Israel found that hs-CRP correlated significactly with all the components of the syndrome in both men and women, but the highest correlation was between waist circumference and hs-CRP **[52]**. From this the authors concluded that waist circumference is the component of the syndrome that most influences the low-grade inflammatory response. They also made the point that, according to their findings, also overweight and obese individuals without the syndrome were at an increased risk for cardiovascular disease.

A German population-based study (using BMI and not waist circumference), concluded that there was a positive and statistically significant trend in levels of CRP with increasing numbers of components of the metabolic syndrome in their population ($P<0.0001$). The age-adjusted geometric means of CRP concentrations in subjects grouped according to the presence of 0-1, 2-3 and ≥ 4 features of the metabolic syndrome were 1.11, 1.27, and 2.16 mg/L, respectively. There was also a statistically significant

crude correlation between CRP and triclygerides (R=0,19), BMI (R=0,32) and glucose (R=0,11) **[53]**.

3.3.3 Can hs-CRP predict the presence of the metabolic syndrome?

Researchers have proposed adding hs-CRP as a clincal criterion for the metabolic syndrome **[54]**. The reasons given for this was that it has been shown to be a consistent prognosticator of cardiovascular and diabetes risk, and is practical in clinical settings.

A cross-sectional screening study done in the Netherlands evaluated the use of hs-CRP to discriminate between centrally obese people with and without the syndrome **[55]**. They concluded that hs-CRP has limited capacity to predict the precence of the metabolic syndrome in people with central obesity. With a cut-off point for hs-CRP at 1.0 mg/L the sensitivity was 82%, the specificity 24%, the positive predictive value 38%, and the negative predictive value 71%. With a cut-off point at 3.0 mg/L the sensitivity was 37%, the specificity 72%, the positive predictive value 42% and negative predictive value 67%. The median hs-CRP levels were significantly higher in people with abdominal obesity with the metabolic syndrome than without it. As the numbers of components of the syndrome increased, so did the median hs-CRP levels. Only waist circumference and triglyceride levels showed a significant independent association with hs-CRP. They concluded that the degree of central obesity seemed to be the main determinant of increased hs-CRP levels. The levels of hs-CRP were higher in centrally obese people with the syndrome than those without it, but it could not be used to diagnose centrally obese people with the metabolic syndrome in this study.

An Italian population based cohort, with healthy middled-aged subject without any components of the metabolic syndrome at

baseline, found that higher baseline CRP values indicated increased risk of developing the syndrome, independently of weight gain. They concluded that the optimal cut-off point of baseline CRP values was 2.1 mg/L, with 86% sensitivity and 75% specificity in detecting the syndrome **[56]**.

4.0 Discussion

4.1 Is adipose tissue dysregulation the key to low-grade inflammation in abdominal obesity?

Several studies shows that there seems to be a close relationship between increased amounts of abdominal/visceral fat, metabolic disturbances and cardiovascular disease. This is an already established connection. Both patients and physicians know this. The question is why? A lot of research data supports that obesity is associated with inflammatory changes in the body, and that these changes are accompanied with increased levels of C-reactive protein. These levels appear to become higher as the abdominal fat mass increases. Waist circumference seems to be the only component that has been independently associated with hs-CRP in a number of studies. This tells us that the theory of fat tissue dysregulation is a plausibel one, and the data seems to support it. However, this area of research is still new and the picture is perhaps not complete. It is very likely that new adipokines will continue to be discovered, and with that new connections and functions come to light. Interleukin-6 is produced by other cells and not adipocyte-specific (like adiponectin), so no conclusions can be drawn until more research is done.

4.2 Hs-CRP - does it add information beyond the metabolic syndrome criteria?

Hs-CRP has many positive attributes. It is inexpesive, non-invasive, does not require fasting and is widely available to name a few. The question is, what can the test tell us that the criteria can not? The increased risk for diabetes and cardiovascular disease is a given, since the definition is a cluster of risk factors for these diseases. The

linear increase in hs-CRP with increasing numbers of components of the metabolic syndrome is therefore not unexpected.

Most of the factors that have been found to correlate with hs-CRP are easy to measure in family/general practice, like abdominal obesity, elevated blood pressure, low LDL and elevated triglycerides and fasting glucose. Hs-CRP does not seem to add any information to the formal criteria here. Hs-CRP also seems to be related to components of the metabolic syndrome that are not as easy to evaluate in family/general practice, like insulin resistance and impaired fibrinolysis. We know that insulin resistance is a key part of the syndrome, and since there is currently no validated test for measuring insulin resistance in a clinical setting, this should be further investigated.

The presence of low-grade inflammation indicated by an elevated hs-CRP level in abdominally obese patients with or without the syndrome indicates that these patients could be at an increased risk for diabetes and cardiovascular disease, and should so be subject to early interventions such as lifestyle change. But the presence of abdominal obesity in itself tells us that lifestyle changes should be made. This is nothing new. If the patient fulfill more of the syndrome criteria, these should be treated like they would in any other patient.

The research data shows that hs-CRP could possibly add some prognostic information, but how to interpret this information without formal guidelines and reference values for this syndrome is a problem. If the hs-CRP values are slightly higher than normal it could indicate increased risk, but it could also mean that the CRP concentration is returning to normal after an infection or after tissue damage. To establish this it is important that the test is repeated to validate the finding.

5.0 Conclusion

Many years may pass from the development of insulin resistance to clinical manifestations of diabetes and cardiovascular disease become apparent. Given the high prevalence of the metabolic syndrome, it is essential that patients with the metabolic syndrome are identified so that the development of diabetes and cardiovascular disease can be prevented. The different definitions in use make this a challenge, but since they are quite similar it is not an impossible task. A measuring tape, a sphygmomanometer, a stethoscope and a venous blood sample can make all the difference in the world to the patient involved.

Whether or not we should add hs-CRP to the list of blood tests is as of now a clinical jugdement for the physician to make, as there are no formal guidelines regarding the metabolic syndrome. Hs-CRP does not appear to be a useful diagnostic tool since it has not been shown to reliably predict the precence of the metabolic syndrome in people with abdominal obesity. However, hs-CRP levels appear to become higher as the abdominal fat mass increases, and waist circumference seems to be the only component that has been independently associated with hs-CRP. This tells us that the theory of fat tissue dysregulation is a plausibel one, but since so many known, and probably unknown, factors interact it is not possible to draw any conclusions without further study.

The problem of how to interpret the findings seems to be the most important point against using the hs-CRP in screening or risk assessment today, as there are no guidelines or verified reference areas for the metabolic syndrome. More research is needed before hs-CRP can be considered as a tool to asess the risk for the development of the metabolic syndrome in apparently healthy abdominally obese people.

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