OBESITY AS AN INFLAMMATORY CONDITION

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ABSTRACT

The prevalence of obesity has increased dramatically in the past decade. This foreshadows an increase in the rates of morbidity and mortality from obesity-related diseases. Research is more frequently proposing that obesity may be seen as a factor linking chronic, systemic inflammation and atherosclerosis. C-reactive protein is an acute phase reactant and a sensitive marker for acute and chronic inflammation of diverse causes. Human adipose tissue expresses interleukin-6, a cytokine that activates the production of C-reactive protein from the liver, potentially inducing low-grade systemic inflammation in persons with excess body fat. This could explain the increased risk of diabetes, heart disease and many other chronic diseases in the obese. This paper aims to provide a review on obesity as an ever-growing epidemic and the possible role that chronic systemic inflammation might play in contributing to the risks associated with one of the most common public health problems.

OPSOMMING

Die voorkoms van obesiteit het oor die afgelope dekade dramaties gestyg en daarmee saam die voorspelling van 'n toename in morbiditeit sowel as mortaliteit as gevolg van obesiteit-verwante siektetoestande. Navorsing dui al hoe meer daarop dat obesiteit moontlik as die skakel kan dien tussen kroniese sistemiese inflammasie en arteriosklerose. C-reaktiewe proteïen is 'n akute fase-reaktant en is 'n sensitiewe merker vir akute sowel as kroniese inflammasietoestande. Interleukien-6 is 'n sitokinien wat hoofsaaklik in vetweefsel geproduseer word. Dit aktiveer die produksie van C-reaktiewe proteïen deur die lewer, met die potensiële gevolg van laegraadse sistemiese inflammasie by persone met oormatige liggaamsvet. Die verskynsel kan moontlik die verhoogde risiko vir diabetes mellitus, koronêre hartsiektes en al die ander kroniese toestande wat voorkom by obesiteit verduidelik. Die doel van hierdie artikel is om 'n oorsig te bied op die groeiende epidemie van obesiteit en die moontlike rol wat kroniese sistemiese inflammasie speel in die bydrae tot die risiko's wat geassosieer word met een van ons mees algemene publieke gesondheidsprobleme.

INTRODUCTION

Famine has been a prominent hazard to human health throughout history, and for thousands of years the link between infection and poor nutrition has been well recognised. Today this threat is as widespread as ever, and there are approximately one billion undernourished individuals worldwide (Blackburn, 2001:397-401). In the past century, however, the pendulum has also swung in the opposite direction, and now as many if not more people are overweight or obese (Cummings & Schwartz, 2003:453-471).

In all populations, developed and developing, rural and urban, obesity is increasing. From 1976 to 1980, 43.8% of African-American women and 25.2% of Caucasian-American women were reported to be overweight or obese in the United States of America (USA) (Dustan, 1990:396) (Figure 1). According to the third National Health and Nutrition Examination Survey (NHANESS III), more than 55% of Americans are overweight or obese and obesity has increased by 30% during the last 50 years, while most of Europe has seen a 10 – 40% increase in obesity during the last ten years (Willett, Dietz & Colditz, 1999:427; Field, Coakley, Must, Spadano, Laird, Dietz, Rimm & Colditz, 2001:1581). In the South African Demographic and Health Survey, it was found that 56.6% of women were overweight or obese (Puoane, Steyn, Bradshaw, Laubscher, Fourie, Lambert & Mbananga, 2002:1041) and Mollentze, Moore, Steyn, Joubert, Steyn, Oosthuizen and Weich (1995:93) found that the prevalence of obesity in Africans is as high as 54.3% among 45-54 year old South African women.

Obesity appears to have been uncommon in Western populations until the time of the Industrial Revolution, when there were increases in urbanisation and a decrease in physical activity (Walker, 1995:1070). Among sub-Saharan Africans in general, a generation or so ago there was very little gain in weight or in blood pressure, with age. Even at present, in most populations, especially in the indigent masses, obesity prevalence remains very low at 1-5%. However, in South Africa and some neighbouring countries like Botswana, Namibia and Zimbabwe (Table 1), with the rise in socio-economic status, urbanisation, and diminishing physical activity, the proportion affected has increased (Walker, Adam & Walker, 2001:368).

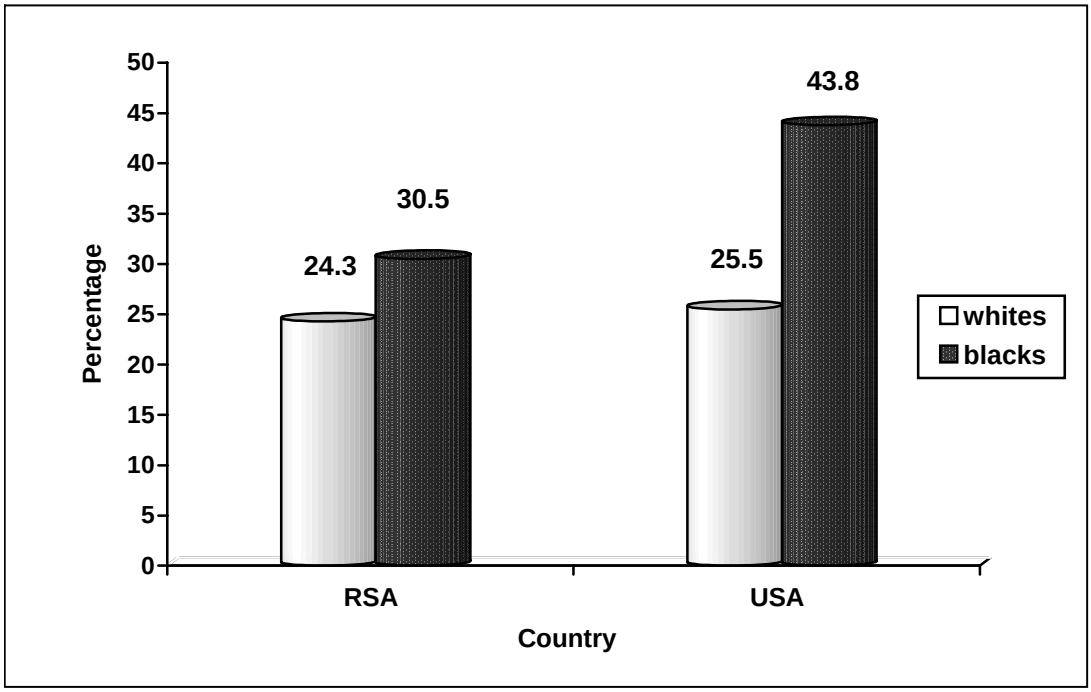
In numerous countries worldwide, such have been the increases, especially in Western populations and especially in women, that according to the World Health Organization (WHO), by the year 2025, 300 million people are likely to be obese (WHO, 1998:132).

The apparent marked excess of obesity among African women (Van Italie, 1985:983) is of particular interest because it parallels the marked African female excess of several obesity-related risk factors and health outcomes (Kumanyika, 1987:45). It has been speculated that even severe obesity in African women may be far less detrimental than in Caucasian women (Walker & Segal, 1980:263; Walker, Walker, Walker & Vorster, 1989:227). Although some research groups (Walker *et al.* 1989:228) have regarded obesity in African women as “healthy obesity”, a South African study showed an unexpectedly high prevalence of hypertension and moderate-risk hypercholesterolemia in an African population, in which a high prevalence of obesity was also found (Mollentze *et al.* 1995:95).

Obesity risks of African women may be enhanced by the presence of multiple risk factors (Kumanyika, 1987:45). Along with obesity, elevated blood pressure and mortality due to heart disease, stroke, and diabetes occur in African women at rates that are 1.5 to 2.5 times the rates in Caucasian women. Across the board, African women are more frequently classified as overweight than Caucasian women in a ratio approaching or exceeding 2:1 (Kumanyika, 1987:32).

Diabetes is more common in Africans than it is in Caucasians (Dustan, 1990:398) and this may explain part of the difference in the prevalence of hypertension between them. Ethnic differences in mortality, from selected diseases including diabetes are of interest. As seen from Table 2, mortality among Africans is greater than among Caucasians for all of the listed diseases. It would be of interest to focus on diabetes mellitus for which death rates of African women are highest of all. This may relate to the increased prevalence of obesity among African women (Dustan, 1990:398).

On the question of causes, no clear mechanism for the excess obesity in African women can be identified. To prevent and treat obesity, especially in African women, more should be known about the underlying causes of obesity among these women to develop ap-



* Overweight is defined as a body mass index (kg/m²) = 27.3 for women
# National Health and Nutrition Examination Survey 1976-1980, Vital and Health Statistics Series II, Number 238, National Center for Health Statistics.

Figure 1: Percentage of overweight or obese females in South Africa and the USA, according to NHANESS II and the South African Demographic and Health Survey. Adapted from Dustan (1990:396) and Puoane *et al*. (2002:1047).

Table 1: Body mass index and percentages of obese African women

Country	BMI*	Obese (%)
Namibia	22.5 ± 4.4	7.1
Zimbabwe	23.1 ± 3.7	5.7
Tanzania	21.7 ± 3.0	1.9
South Africa	*28.0 ± 6.2*	*32.0*
Rural Zulu	-	31.6
Rural Venda	25.4 ± 4.2	19.9
Jhb. Squatters	29.8 ± 7.2	33.3
Cape Town	27.8 ± 6.2	34.4
Durban	26.6 ± 5.0	22.6
Qwa Qwa Africans	28.9 ± 7.0	38.4
Mangaung Africans	29.6 ± 7.4	43.5
North West Africans	26.9 ± 6.8	28.6

* BMI = body mass index

Adapted from Walker *et al*. (2001:369), Mollentze *et al*. (1995:93) and Kruger, Venter and Vorster (2001:735).

Table 2: Race differences in mortality from cardiovascular diseases in women in the USA*

	Black women	White women
All causes	589.1	390.6
Major cardiovascular diseases	250.5	157.4
Ischemic heart disease	100.8	82.9
Stroke	50.3	27.9
Hypertension	5.2	1.2
Diabetes mellitus	21	8.1

* The figures are age-adjusted deaths/100,000 Adapted from Dustan (1990:398).

propriate and culturally accepted interventions.

With the advent of this chronic metabolic overload, a new set of problems and complications at the intersection of metabolism and immunity has emerged, which includes the obesity-linked inflammatory diseases diabetes and atherosclerosis (Hotamisligil, 2004:953-962). There is now considerable evidence supporting the idea that obesity is, in fact, an inflammatory condition.

Crucial questions that are currently open regard the initiation of the inflammatory response. How and why does the body initiate an inflammatory response to obesity? Does obesity per se induce an inflammatory response, or is inflammation initiated as a secondary event by hyperlipidemia or hyperglycemia?

The aim of this review article is to point out how obesity can be described as an inflammatory condition, which may partly be the mechanism for the development of non-communicable diseases.

PATHOPHYSIOLOGY OF OBESITY

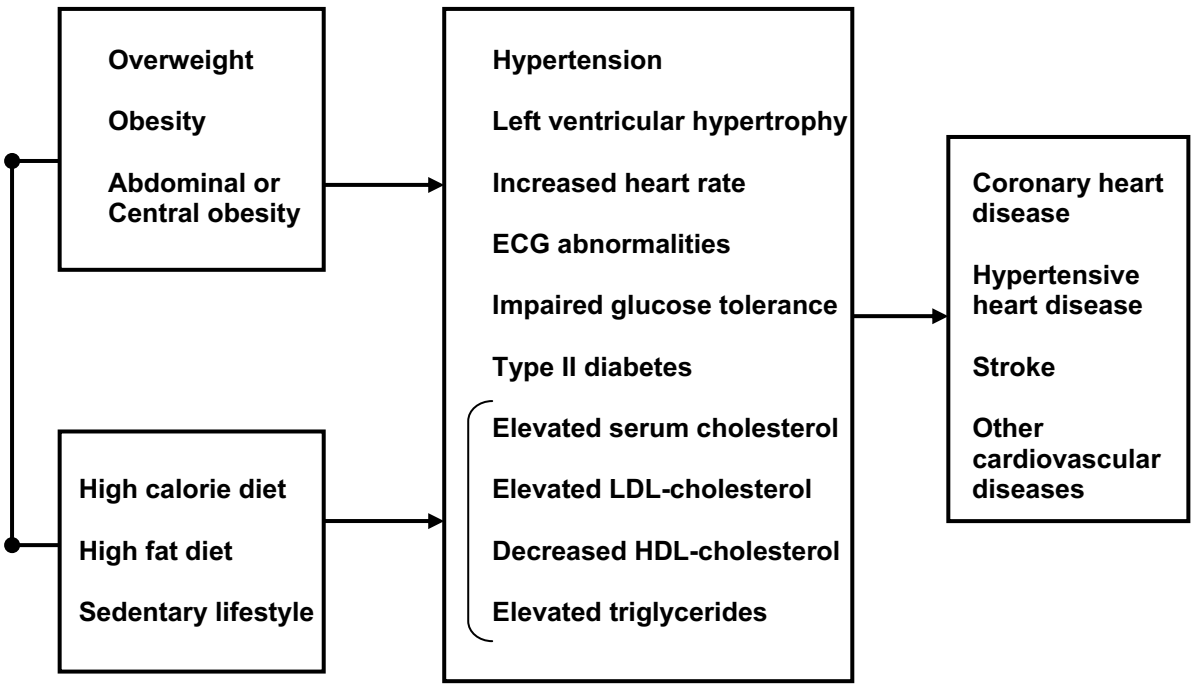
It is clear from the literature that obesity is a critical public health problem. Obesity is classified as a body mass index (BMI) of 30 kg/m² or more and it is functionally defined as the percent body fat (32%) (Lohman, 1992:80) at which disease risk increases (Figure 2) (Kumanyika & Adams-Campbell, 1991:48). Obesity is an underlying factor in many diseases but the factors responsible for the causation of obesity are poorly understood. Environmental, behavioural, and genetic factors have been shown to contribute to the development of obesity (Pi-Sunyer, 2002:975).

Genetics versus environment

The relative contributions of genetics and environment to the etiology of obesity have been evaluated in many studies. Although it varies from study to study, approximately 30%-40% of the variance in BMI can be attributed to genetics and 60%-70% to environment. The interaction between genetics and environment is also important. In a given population, some people are genetically predisposed to develop obesity, but that genotype may be expressed only under certain adverse environmental conditions, such as high-fat diets and sedentary lifestyles (Stunkard, 1988:902-23)

Metabolic predictors

The development of obesity occurs when the caloric intake is disproportionate to the energy expended. Three metabolic factors have been reported to be predictive of weight gain: low adjusted sedentary energy expenditure, a high respiratory quotient, and a low level of spontaneous physical activity. Several other factors also are associated with overweight but it is not clear why or how they have an impact. Sex, age, race, and socioeconomic status have an impact on weight gain, with overweight and obesity being more likely among women, older individuals, members of minority races, and those of low socioeconomic status (Pi-Sunyer, 2002:995).



* ECG = Electrocardiogram

\# Low density lipoprotein

High density lipoprotein

Adapted from Kumanyika & Adams-Campbell (1991:48).

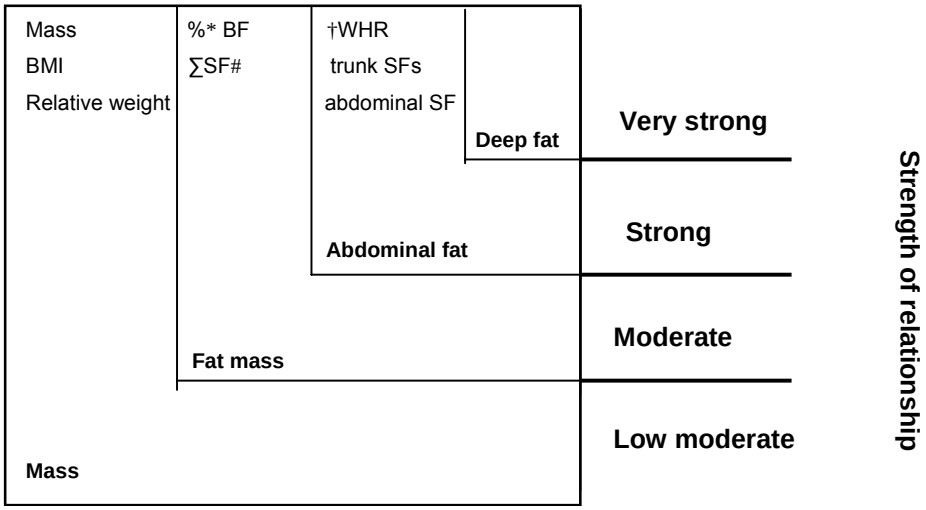
Figure 2: Weight-related variables with established relations cardiovascular disease risk factors, morbidity or mortality

ABDOMINAL OBESITY

Abdominal obesity is identified as an independent risk factor for CHD in both men and women (Lapidus, Bengtsson, Larsson, Pennert, Rybo & Sjostrom 1984:1260) and in both African and Caucasian subjects (Folsom, Burke, Byers, Hutchinson, Heiss, Flack, Jacobs & Caan, 1991:1610S). While BMI reflects general obesity, waist circumference (WC) and waist-hip-ratio (WHR) are related to central-type obesity, where body fat is primarily located in the abdomen. Prospective epidemiological studies have revealed that central obesity (determined by WC and WHR) conveys an independent prediction of coronary artery disease risk and is more relevant compared to general obesity (determined by BMI) (Folsom, Kaye, Sellers, Hong, Cerhan, Potter & Prineas, 1993:486).

High levels of deep abdominal fat is characteristic of adult-onset obesity and has been associated with diabetes, hyperlipidemia, hypertension, heart disease, stroke and other diseases in several populations (Okosun, Rotimi, Forrester, Fraser, Osotimehin, Muna & Cooper, 2000:180; Lemieux, Pascot, Prud'Homme, Alméras, Bogaty, Nadeay, Bergeron & Després, 2001:965). Bergstrom, Leonetti, Newel-Morris, Shuman, Wahl and Fujimoto (1990:491-493) reported that even when the effects of glucose tolerance and BMI were accounted for, males with clinical CHD had more deep abdominal fat than their sub-clinical counterparts (Figure 3).

Cox, Whichelow, Ashwell, Prevost and Lejeune (1997:677) and Guagnano, Ballone, Merlitti, Murri, Pace-Palitti, Pilotti and Sensi (1997:634), who reported that indices of abdominal obesity were more strongly asso-



* BF = body fat; # SF = skinfold; † WHR = waist-hip-ratio.

Figure 3: Relationship of anthropometric measures to risk factors for major pathologies as illustrated by Norton and Olds (1996:367).

ciated with blood pressure than BMI, found a positive correlation of both WC and WHR with blood pressure. More evidence for the harmful effects of abdominal obesity became available from the Nurses' Health Study in which it was found that a higher WC was associated with an increased risk of CHD, even after controlling for BMI (Rexrode, Carey, Hennekens, Walter, Colditz, Stampfer, Willet & Manson, 1998:1846).

OBESITY AND CARDIOVASCULAR DISEASE

Obesity places a heavy burden on the entire cardiovascular system, contributing to considerable overall morbidity and mortality (Figure 2).

Obesity has adverse effects on several coronary artery disease (CAD) risk factors. Obese patients are more likely to be hypertensive than lean patients, and weight gain is typically associated with increases in arterial pressure (Lavie & Messerli, 1986:275-279), and independent of arterial pressure, obesity increases the risk of left ventricular hypertrophy (LVH) (Lavie, Venture & Messerli, 1992:134-143). Obesity also adversely affects plasma lipids, especially increasing triglycerides and decreasing the cardio protective levels of high-density lipoprotein cholesterol, and is the major contributor to adult-onset diabetes mellitus and the insulin resistance syndrome, which are associated with high levels of inflammation and overall cardiovascular mortality (Lavie & Milani, 1997:397-401). Despite adversely affecting these risk factors, including markedly increasing levels of high sensitivity CRP (Lavie, Milani & Morshedi, 2003:177A-178A), data from the Framingham Heart Study have indicated that obesity is an independent risk factor for major CAD events in men and, particularly, in women (Hubert, Feinleib, McNamara & Castelli, 1983:968-977).

Obesity has been hypothesised to induce LVH by various mechanisms. One important mechanism may be related to the increased circulatory blood volume of obesity. As a consequence, cardiac output increases because of an increase in stroke volume. The increases in circulating blood volume and cardiac output produces an increase in left ventricular cavity size, which produces an increase in left ventricular wall stress in accordance with Laplace's law (Abate, 1999:12).

In addition to increasing eccentric LVH and the propensity for more complex dysrythmias, obesity also has adverse effects on cardiac function. In a study of 74 morbidly obese patients Alpert, Terry, Mulekar, Cohen, Massey, Fan, Panayiotou and Mukerji (1997:736-740), demonstrated that nearly one-third had clinical evidence of heart failure (HF) and the probability of HF increased with increasing duration of morbid obesity. The increase of sudden death in the obese may also be the result of cardiac electrical abnormalities. The primary electrical abnormality described in obese patients is prolonga-

tion of the QT interval. Moreover, sleep apnea, which is often found in obese patients, may also contribute to sudden arrhythmia (Abate, 1999:12).

ADIPOSE TISSUE AND INFLAMMATORY MARKERS

The adipocyte is another important component of inflammation. Until relatively recently adipose tissue was considered a passive storage depot for fat but is now known to play an active role as an endocrine organ in metabolism (Flier, 1995:15). This remarkable understanding is allowing us to more clearly define the role adipocytes play in health and in obesity and how inflammatory mediators act as signalling molecules in this process.

The adipocyte secretes a number of factors characterised as either pro- or anti-inflammatory (Finegood, 2003:S5). The normal inflammatory response relies upon metabolic support and energy redistribution, particularly the mobilisation of stored lipid, plays an important role in fighting infection during the acute-phase response (Khovidhunkit, Kim, Memon, Shigenaga, Moser, Feingold & Grunfeld, 2004:1169-1196). More than a decade ago the first molecular link between inflammation and obesity – TNF-á – was found to be overproduced in the adipose as well as muscle tissues of obese humans (Hotamisligil, Arner, Caro, Atkinson & Spiegelman, 1995:2409-2415).

Tumor necrosis factor-á

TNF-á is a multi-functional circulating pro-inflammatory cytokine derived from endothelial and smooth muscle cells, as well as macrophages. TNF-á plays a major role in the cytokine cascade as it stimulates the synthesis of other cytokines like interleukin-6 (IL-6), which is a central mediator of the acute-phase response and the primary determinant of C-reactive protein (CRP) production (Heinrich, Castell & Andus, 1990:621-636; Van Snick, 1990:253-278), thereby contributing to the maintenance of a chronic low-grade inflammation state involved in the progression of obesity and its associated co-morbidities (Bulló, Garcia-Lord, Megias & Salas-Salvadó, 2003:528).

Interleukin-6

The reason for increased production of CRP in obesity is most likely due to the action of IL-6. IL-6 is a cytokine produced in the adipose tissue of healthy humans. It is released into the circulation and activates the production of CRP from the liver and CRP levels are a direct indicator of IL-6 levels in vivo (Mohamed-Ali, Coodrick, Rawesh, Katz, Miles, Yudkin, Klein & Coppack, 1997:4199; Fried, Bunkin & Greenberg, 1998:849). IL-6 is believed to represent the major regulator of the hepatic acute phase response (Bataille & Klein, 1992:982-983) so that a substantial contribution to circulating levels from adipose tissue may mean that obesity can resemble a low-grade inflammatory state (Yudkin, Kumari, Humphries & Mohamed-Ali, 2000:211).

Approximately 25-30% of serum IL-6 originates from adipose tissue and the secretion of IL-6 from subcutaneous fat is in proportion to fat mass (Mohamed-Ali *et al.* 1997:4199). Omental fat cells secrete approximately two to three times more IL-6 compared to subcutaneous adipocytes (Fried *et al.* 1998:848). Therefore, subjects with more abdominal fat may have increased IL-6 and CRP, which could partially account for increased mortality rates in abdominally obese subjects if IL-6 or CRP contributed to disease promotion (Heilbronn & Clifton, 2002:317).

Although little is known about the effects of IL-6 on adipose tissue, one possible action is a down-regulation of adipose tissue lipoprotein lipase (Greenberg, Nordan, McIntosh, Calvo, Scow & Jablons, 1992:4115). The regulated production of this multifunctional cytokine may modulate regional adipose tissue metabolism and may contribute to the recently reported correlation between serum IL-6 and the level of obesity (Fried *et al.* 1998:850).

C-reactive protein

C-reactive protein (CRP) is an acute phase reactant, synthesised primarily in hepatocytes and secreted by the liver. It is regulated by a variety of inflammatory cytokines of which interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-á) are mainly involved (Heilbronn & Clifton, 2002:316-319).

CRP has a normal range of < 2 mg/l in populations without evidence of acute illness (Gabay & Kushner, 1999:452). Therefore, enhanced levels of CRP can be

used as a sensitive marker of systemic inflammation (Das, 2001:954). Pannacciulli, Cantatore, Minenna, Bellacicco, Giorgino and De Pergola (2001:1418) found four factors - age, insulin resistance, central fat accumulation and the amount of total body fat to be the most powerful predictors of CRP concentrations in apparently healthy adult women. Recently CRP concentrations have been shown to be significantly associated with several cardiovascular risk factors, such as age, smoking, hypertension, exercise, plasma lipids, homocysteine and BMI (Rohde, Hennekens & Ridker, 1999:1021).

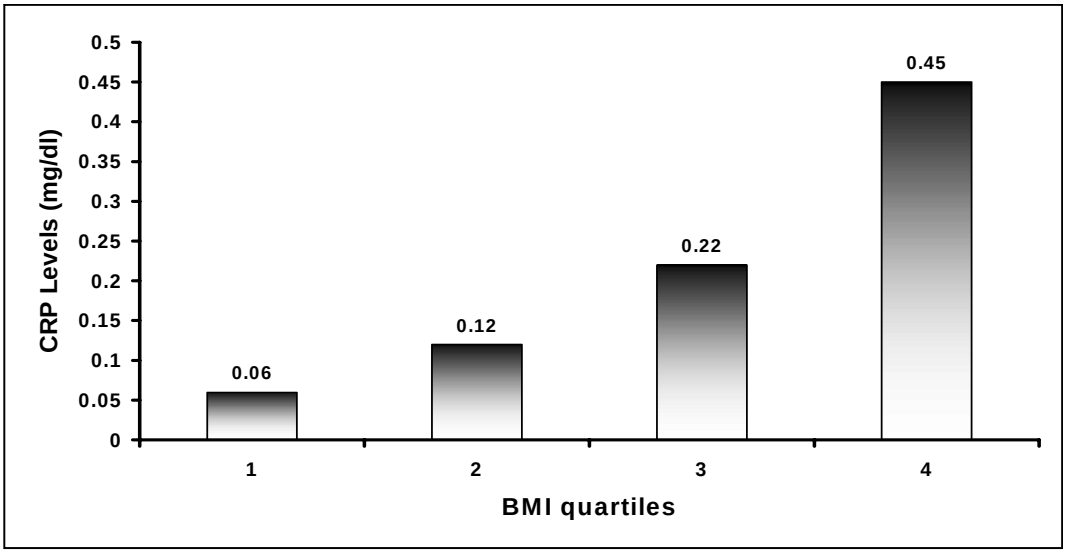
Concerning the relationship between CRP concentration and BMI level, it was found that the prevalence of elevated CRP levels (concentrations = 22 mg/l) is higher in both overweight (BMI 25-29.9 kg/m²) and obese (BMI = 30 kg/m²) patients than in normal weight (BMI < 25 kg/m) subjects (Visser, Bouter, McQuillan, Wener & Harris, 1999:2133). Even moderately elevated CRP plasma concentrations have been associated with a significant increase in risk of future myocardial infarction, stroke and peripheral atherosclerosis among apparently healthy middle-aged men and women (Ridker, Cushman, Stampfer, Tracy & Hennekens, 1998:427; Ridker, Buring, Shih, Matias & Hennekens, 1998:732) even after adjustment for known cardiovascular risk factors (Rohde *et al.* 1999:1021).

In particular, CRP concentrations have been recently demonstrated to be as strong as apolipoprotein B-100 levels and TC/HDL-C ratio in predicting the risk of cardiovascular events in women and even stronger than concentrations of TC, HDL-C, lipoprotein(a) and homocysteine (Ridker, Hennekens, Buring & Rifai, 2000:842). This may explain the increased risk of diabetes, heart disease and many other chronic diseases in the obese.

In a study by Rexrode *et al*. (2003:7), BMI was the strongest predictor of elevated inflammatory markers (Figure 3). The associations with BMI were dramatic; women in the highest BMI quartile (BMI = 28.3 kg/m²) had a more than twelve-fold increased risk of having elevated CRP levels and a more than four-fold increased risk of elevated IL-6 levels and higher CRP and IL-6 levels were observed with each increment in BMI (Figure 4).

Adipose tissue

Pannacciulli *et al*. (2001:1419) hypothesised that adipose tissue is responsible for a mild, chronic inflammatory state, as expressed by levels of CRP, IL-



* quartile 1 (< 22.4); quartile 2 (22.4- < 24.6); quartile 3 (24.6- < 28.3); quartile 4 (= 28.3)

Adapted from Rexrode, Pradhan, Manson, Buring & Ridker (2003:5).

Figure 4: Median CRP levels by BMI quartiles* in women

6 and TNF-á, which may induce insulin resistance and endothelial dysfunction, therefore leading to atherosclerosis as proposed by Yudkin, Stehouwer, Emeis and Coppack (1999:977).

Human abdominal visceral adipose tissue has been reported to release more IL-6 compared to subcutaneous adipose tissue (Fried *et al.* 1998:849) thereby explaining the results of Pannacciulli *et al*. (2001:1419) that WC is a stronger predictor of CRP concentrations than total fatness, expressed as BMI or fat mass.

These findings fit well with a growing body of evidence implicating adipose tissue in general and visceral adiposity in particular as key regulators of inflammation. Although subcutaneous fat clearly plays an important role, Tracy (2001:881) found the identification of visceral adiposity to be a key correlate of CRP in men, which is consistent not only with the emerging role of abdominal fat in the metabolic syndrome (Montague & O'Rahilly, 2000:886) but also with the concept of "non-overweight obesity" as proffered by Dvorak and colleagues (Dvorak, Denino, Ades & Poehlman, 1999:2213). They suggested that the role of visceral fat may be more complex than suspected, because even people who are not obviously overweight may still have disproportionately too much visceral fat, with the result of a predisposition toward insulin resistance and atherosclerotic disease, possibly through inappropriate cytokine secretion (Tracy, 2001:882).

If true, this concept begs the question of whether the key variable might not be disproportionate visceral adiposity rather than what has traditionally been considered obesity as characterised by weight, WC, or BMI (Tracy, 2001:882). It is suggested that adiposity and in particular visceral adipose tissue is a key promoter of low-grade chronic inflammation (Forouhi, Sattar & McKeigue, 2001:1331).

Assays of inflammatory markers

Both TNF-á and IL-6 are measured by enzyme-linked immunosorbent assay (ELISA) for in vitro quantitative determination of TNF-á and IL-6, respectively, in human serum, plasma or buffered solutions of cell culture medium (Diaclone, Gleming, France). Monoclonal antibodies specific for TNF-á or IL-6 is used in these assays. CRP is measured by a high sensitivity test (CardioPhase hsCRP, Dade Behring, Marburg, Germany) for the quantitative determination of CRP in human serum or plasma by means of enhanced immunonephelometry, using monoclonal antibodies to CRP.

ATHEROSCLEROSIS AS AN INFLAMMATORY DISEASE

Elevated lipid levels are characteristic of obesity, infection and other inflammatory states. Hyperlipidemia in obesity is responsible in part for inducing peripheral tissue insulin resistance and dyslipidemia and contributes to the development of atherosclerosis (Wellen & Hotamisligil, 2005:1112). It is interesting to note that metabolic changes characteristic of the acute-phase response are also proatherogenic; thus, altered lipid metabolism that is beneficial in the short term in fighting against infection is harmful if maintained chronically (Khovidhunkit *et al.* 2004:1169-1196).

Atherosclerosis is accelerated both directly by effects of cytokines on endothelial cells and indirectly by cytokine effects on the liver, causing increased production of CRP and related factors (Libby & Ridker, 1999:148-1150). The chronic inflammatory process involving the arterial endothelium that ultimately results in the complications of atherosclerosis may be caused by a response to the oxidative components of modified low-density lipoprotein (LDL), chronic infection or even free radicals (Paoletti, Gotto & Hajjar, 2004:III-20). Atherosclerosis is a multi-factorial, multi-step disease that involves chronic inflammation at every stage, from initiation to progression and, eventually, plaque rupture (Libby, Ridker & Maseri, 2002:1135-1143).

In atherosclerosis, the normal homeostatic functions of the endothelium are altered, promoting an inflammatory response (Prescott, McIntyre, Zimmerman & Stafforini, 2002:727-33). The association of inflammation with the initiation and progression of atherosclerosis suggest that markers of inflammation like CRP may be useful in predicting an increased risk of coronary heart disease.

In a review by Lind (2003:208), the idea that circulating biomarkers of inflammation are associated with atherosclerotic diseases as well as with acute coronary

syndromes, indicative of plaque rupture, is supported. It is, however, a question whether or not these markers of inflammation really are markers or if they are actively involved in the atherosclerotic process. CRP has been detected in early human atherosclerotic plaques (Torzewski, Torzewski, Bowyer, Frohlich, Koenig, Waltenberger, Fitzsimmons & Hombach, 1998:1386-92), and its appearance in plaques has been related to the intima-media thickness of the carotid arteries (Zhang, Cliff, Shoefl & Higgins, 1999:375-9). It has been shown that IL-6 gene transcripts are expressed in human atherosclerotic lesions (Rus, Vlaicu & Niculescu, 1996:263-71), and it has also been shown that endothelial expression of adhesion molecules occurs in human atherosclerotic plaques and is an early manifestation of experimental cholesterol-induced atherosclerosis (Davies, Gordon, Gearing, Pigott, Woolf, Katz, & Kyriakopoulos, 1993:223-9). Thus, it appears as if there is some evidences that some of these markers of inflammation could be directly involved in the formation and progression of atherosclerosis, although more definitive proofs yet have to be presented.

INFLAMMATION AND DIABETES

Type II diabetes is a leading cause of morbidity and mortality. Prevention of diabetes and its associated burden, primarily cardiovascular morbidity and mortality, have become major health issues worldwide (Venkat, Gregg, Fagot-Campagna, Engelgau & Vinicor, 2000:S77-S84). Although type II diabetes was characterised as a disease associated with insulin resistance even before insulin could be measured in the blood, the central importance of insulin resistance was not fully recognised until the early 1980's (Bergman, Finegood & Ader, 1985:45-86). Numerous studies documented the inverse relationship between body mass index and insulin sensitivity suggesting that obesity is a cause of insulin resistance. While increasing body fat was associated with decreasing insulin sensitivity, the muscle mass was thought to be central to insulin resistance given its relative size and significant contribution to glucose utilisation. That signalling molecules secreted by adipose tissue played a major role in this insulin resistance was first appreciated in the mid-1990s with the discovery of leptin (Finegood, 2003:S4). That other secretory products of the adipocyte, including the inflammatory cytokine TNF-á, might control insulin sensitivity was suggested by the work of Hotamisligil, Shargill and Speigelmann (1993:87-91).

In a report by Duncan, Schmidt, Pankow, Ballantyne, Couper, Vigo, Hoogeveen, Folsom and Heiss (2003:1802), consistent with previous investigations of the inflammation-diabetes association, it was demonstrated that sub-clinical elevations of IL-6 and CRP are related to the development of diabetes in middle-aged adults. It is increasingly recognised that a low-grade systemic inflammation precedes and predicts the development of both diabetes and atherothrombotic diseases. New facts that may explain this association are emerging. The mild inflammatory state is closely related to obesity and insulin resistance. Adipocytes, especially in the obese, secrete a number of pro-inflammatory cytokines (Trayhurn & Beattie, 2001:329-39), some of which have been shown to directly inhibit insulin signalling (Uysal, Wiesbrock, Marion & Hotamisligil, 1997:610-4).

Crook, Tutt and Pickup (1993:57-60), first proposed that type II diabetes was also an inflammatory condition characterised by elevated concentrations of acute phase inflammatory reactants in the plasma. These data have been confirmed by several studies reinforcing the idea that type II diabetes is an inflammatory condition.

The fact that obesity, a major risk factor for type II diabetes, and diabetes itself, are inflammatory conditions, led to investigations exploring whether inflammatory mediators predict the development of type II diabetes in populations at risk. Several such studies have now confirmed that the presence of inflammation predicts the development of type II diabetes. The first of these studies by Schmidt, Duncan, Sharrett, Lindberg, Savage, Offenbacher, Azambuja, Tracy and Heiss (1999:1649-52), showed that the presence of inflammatory mediators predicted the future occurrence of type II diabetes in adults and was part of the larger ARIC study. A recent paper from the same study continues this theme by showing that elevated plasma concentrations of IL-6 and CRP predict type II diabetes (Duncan, Schmidt, Pankow, Ballantyne, Couper, Vigo, Hoogeveen, Folsom & Heiss, 2003:1799-1805).

THERAPEUTIC IMPLICATIONS OF THE EFFECTS OF DRUGS AND EXERCISE

The association of inflammatory markers with increased risk for CHD suggest the use of anti-inflammatory treatment to reduce the risk for future CHD events. However, no prospectively designed studies have so far assessed clinical benefits after specific treatment of these markers. Such studies would indicate whether inflammatory markers could be used not only in risk stratification but also to determine therapeutic efficacy.

The effects of statins on CRP

In several trials, the effects of statins on CRP levels appeared unrelated to their effects on lipid levels, suggesting that statins may exert an anti-inflammatory action (Ridker, Rifai, Pfeffer, Sacks, Moye, Goldman, Flaker & Braunwald, 1998:839-44; Ridker, Rifai, Clearfield, Downs, Weis, Miles, Gotto & Phil, 2001:1959-1965). The well documented lipid-regulating effects of statins in conjunction with their possible anti-inflammatory properties may therefore provide a theoretical double benefit (Gomez-Gerique, Ros, Olivan, Mostaza, Vilardell, Pinto, Civeira, Hernandez, Da Silva, Rodriguez-Botaro, Zambon, Lima, Daz, Aristegui, Sol, Chaves & Hernandez, 2002:245-251).

In the CARE study, it was shown that a statin given for five years reduced CRP-levels compared with placebo (Ridker, Rifai, Pfeffer, Sacks & Braunwald, 1999:230-5) and circulating levels of IL-6 and TNF-á have also been shown to be reduced by treatment with statins (Rosenson, Tangney & Casey, 1999:983-4).

Angiotensin-Converting Enzyme Inhibition

By interrupting the expression of adhesion molecules and cytokines, angiotensin-converting enzyme (ACE) inhibitors exert anti-inflammatory effects on the development of atherosclerosis and on the plaque rupture that initiates acute coronary syndromes (Halkin & Keren, 2002:126-34). In the future, identification of specific markers of inflammation may identify a subpopulation of high-risk post-MI patients and others for whom therapy with an ACE inhibitor will be more effective than it is for the total patient population.

Aspirin or Acetylic-salicylic acid (ASA)

ASA treatment is one of the most established treatments for atherosclerotic complications. Aspirin has anti-platelet and anti-inflammatory activities. The ability of aspirin to decrease the incidence of a first thrombotic event, including myocardial infarction (MI), ischemic stroke, and venous thrombosis, was measured with respect to CRP levels. Men with the highest CRP levels had an increased risk for MI among men in the highest quartile of CRP levels, but not among those in the lowest quartile. This result suggests that the relation of CRP-mediated inflammation to vascular risk is confined to the arterial circulation, that aspirin acts as an anti-inflammatory agent, and that CRP levels may identify persons who are more likely to respond to aspirin therapy (Ridker, Cushman, Stampfer, Tracy & Hennekens, 1997:973-79). Both levels of CRP and IL-6 have been shown to be reduced during ASA-treatment in patients with CAD (Ikonomidis, Andreotti, Economou, Stefanadis, Toutouzas & Nihoyannopoulos, 1999:793-98).

Weight loss and physical activity

Lemieux *et al*. (2001:966) suggest that because of the powerful association with obesity, weight loss may be another method for down regulating an individual's inflammatory status. Heilbronn, Noakes and Clifton (2001:969) studied a group of healthy obese women, characterised by an average BMI of 34 kg/m², with a range of 28 to 44 kg/m². These subjects were placed on a very low fat diet for twelve weeks and an average weight loss of 8 kg was achieved. CRP decreased by 26% and the authors observed a strong correlation between weight loss and change in CRP.

It is suggested by Saito, Ishimitsu, Minami, Ono, Ohrui and Matsuoka (2003:78) that correction of overweight may be effective in reducing plasma CRP. Indeed, in a recent study, Tchernof, Molan, Sites, Ades and Poehlman (2002:567) reported that adiposity was a significant predictor of plasma CRP and that caloric restriction-induced weight loss markedly reduced plasma CRP in obese postmenopausal women. It has also been reported by Smith, Dykes, Douglas, Krishnaswamy and Berk (1999:1725) that moderate exercise reduces inflammation markers. In their study, they reported CRP levels as measured before an exercise programme which ranged from 0 to 0.9 mg/dL in the lower quartile to 5.8 to 37.5 mg/dL in the upper quartile, with a mean value of 4.81 (1.09) mg/dL. Va-

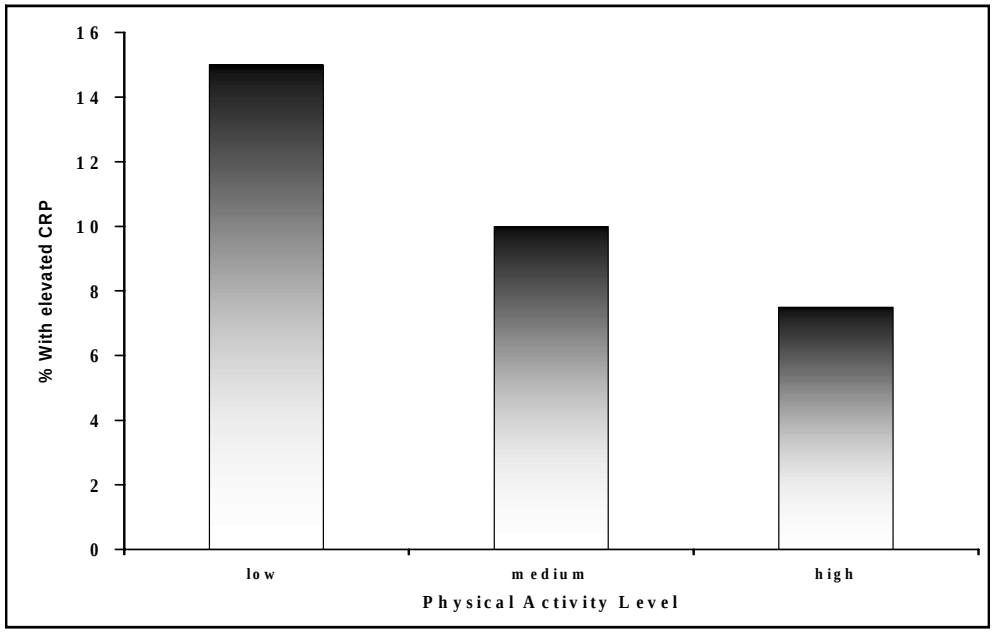
lues taken after the exercise programme decreased by 35% to 3.13 (0.64) mg/dL (P = 0.12) (2-sided t-test). The frequency of values in the upper quartile dropped by 50% after following the exercise programme (P= 0.01).

Tisi, Hulse, Chulakadabba, Gosling and Shearman (1997:347) evaluated several markers of disease severity in a randomised trial of therapeutic exercise training in 49 patients with intermittent claudication. In their findings, serum CRP levels were significantly reduced after 3 to 6 months of regular physical activity. The observation by Rohde *et al*. (1999:1021) that men who exercise regularly were more likely to have lower CRP levels is consistent with the findings of Tisi *et al*. (1997:347), as well as with the known beneficial effects of regular physical activity.

Abramson and Vaccarino (2002:1288-1289) also found that more frequent physical activity is independently associated with lower odds of having elevated inflammation levels among apparently healthy US adults 40 years and older, independent of several confounding factors. They found that among those engaging in low, medium and high physical activity levels, the percentages of persons with elevated CRP levels were 15.1%, 9.7%, and 6.5% respectively. As physical activity levels increased, the odds of having an elevated CRP level significantly decreased independent of other factors (Figure 5).

In another study, Ford (2002:567) found that physical activity is inversely associated with CRP concentrations, suggesting that physical activity may mitigate inflammation. These results add to mounting evidence that physical activity may reduce inflammation, which is a critical process in the pathogenesis of cardiovascular disease. Taken together, these physical and dietary approaches to correct obesity may be promising in inhibiting cardiovascular inflammation and future risk of developing cardiovascular diseases (Saito *et al.* 2003:78).

More and more reports are indicating that markers of inflammation are predictive of increased CHD incidence and mortality, (Rohde *et al.* 1999:1021; Danesh, Whincup & Walker, 2000:199-204) and the development of CHD is increasingly being viewed as an inflammatory process (Ridker *et al.* 1998:733). As such, it might be reasonable to hypothesise that if physical activity lowers CHD risk, it may do so in part by preventing or reducing inflammation. It is not clear how physical ac-



As reported by Abramson and Vaccarino (2002:1289).

Figure 5: Unadjusted percentages of persons with elevated CRP levels according to frequency of physical activity

tivity could influence the specific inflammatory activity associated with cardiovascular disease or other diseases. By reducing adipose mass, physical activity could decrease IL-6 production and hence, CRP production. However, after adjusting for BMI and WHR, CRP concentration was still strongly related to level of physical activity in the study done by Ford (2002:566), suggesting that physical activity influences the inflammatory process through other mechanisms. Geffken, Cushman, Burke, Polak, Sakkinen and Tracy (2001:248) suggest that physical activity can reduce inflammation by improving insulin resistance because concentrations of several inflammatory markers were raised in insulin-resistant subjects.

Assuming physical activity does indeed help prevent or reduce inflammation, what is the mechanism by which it would accomplish this effect? Strenuous physical activity can lead to muscle damage and thereby increase inflammation (Pyne, 1994:55). In contrast, however, there are plausible mechanisms by which physical activity could also reduce inflammation. For example, obesity is a factor that is strongly related to higher levels of inflammation (Visser *et al.* 1999:2135) and it has been suggested that physical activity may reduce inflammation by reducing obesity levels (Geffken *et al.* 2001:248). However, in the study done by Abramson and Vaccarino (2002:1289), it was observed that physical activity was associated with lower levels of inflammation even after adjustment for measures of general obesity (BMI) and central obesity (WHR). Therefore, they found it unlikely that the association between activity and inflammation is mediated entirely by reductions in obesity.

Since elevated levels of CRP and other markers of inflammation have been shown to be important predictors of increased CHD risk (Ridker *et al.* 1998:733), the study by Abramson and Vaccarino (2002:1291) implies, although it does not prove, that physical activity may lower CHD risk by reducing inflammation. Their results suggest that the anti-inflammatory effects of regular physical activity may mediate the association between physical activity and reduced coronary heart disease risk.

SUMMARY

The etiology of obesity represents a complex interaction of genetics, diet, metabolism and physical activity levels. Obesity has been positively associated with increased serum concentrations of vascular inflammatory markers, and adipose tissue has been proposed as a factor directly modulating pro-inflammatory cytokine levels. Individuals with obesity are also at an increased risk for various chronic diseases like diabetes and atherosclerosis which are also characterised by elevated CRP concentrations. Elevated CRP levels have also been independently associated with increased risk of myocardial infarction, ischemic heart disease and peripheral arterial disease.

This is interesting because more frequent physical activity is associated with lower odds of having elevated inflammation levels. Research suggests that the anti-inflammatory effects of regular physical activity may mediate the association between physical activity and reduced coronary heart disease risk.

From the preceding discussion it is evident that low-grade, systemic inflammation occurs in obesity and that weight loss after dietary treatment, as well as regular physical activity may lower CHD risk by reducing inflammation. Studies that examine physical activity as a prospective predictor of inflammation in general population samples are needed to establish whether physical activity truly prevents or reduces inflammation and whether this reduction accounts for the association between increased physical activity and lower CHD risk.

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