Revisión
Hepatic inflammatory biomarkers and its link with obesity and chronic diseases

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Abstract

Introduction: The low-grade inflammation and insulin resistance are two events that could be present in varying degrees, on obesity and chronic diseases. The degree of subclinical inflammation can be gauged by measuring the concentrations of some inflammatory biomarkers, including the hepatic origin ones. Some of those biomarkers are sialic acid, α1-antitrypsin and the C-terminal fragment of alpha1-antitrypsin, ceruloplasmin, fibrinogen, haptoglobin, homocystein and plasminogen activator inhibitor-1.

Objectives: To approach the relation between adiposity and hepatic inflammatory markers, and to assess the possible associations between hepatic inflammatory biomarkers and obesity, as well as their capacity of predicting chronic diseases such as type 2 diabetes and atherothrombotic cardiovascular diseases.

Methods: We used electronic scientific databases to select articles without restricting publication year.

Results: The sialic acid predicts the chance increase to become type2 diabetic independently of BMI. Moreover, the α1-antitripsin, ceruloplasmin, fibrinogen and haptoglobin biomarkers, seem predict the chance increase to become type2 diabetic, dependently, of BMI. So, this process could be aggravated by obesity. The concentrations of fibrinogen, homocystein and PAI-1 increase proportionally to insulin resistance, showing its relation with metabolic syndrome (insulin resistance state) and with type2 diabetes. In relation to cardiovascular diseases, every biomarkers reported in this review seem to increase the risk, becoming useful in add important prognostic.

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Biomarcadores hepáticos de inflamación y su vínculo con la obesidad y las enfermedades crónicas

Resumen

Introducción: El bajo grado de inflamación y la resistencia a la insulina son dos eventos que podrían estar presentes en mayor o menor grado, en la obesidad y las enfermedades crónicas. El grado de inflamación subclínica se puede evaluar por medición de las concentraciones de algunos biomarcadores inflamatorios, incluyendo los de origen hepático. Algunos de estos biomarcadores son el ácido siálico, α1-antitripsina y el fragmento C-terminal de la alfa 1-antitripsina, ceruloplasmina, fibrinógeno, haptoglobina, la homocisteína y el inhibidor-1 del activador del plasminógeno.

Objetivos: Evaluar la relación entre la obesidad y los marcadores de inflamación hepática, y las posibles asociaciones entre los biomarcadores inflamatorios hepáticos y la obesidad, así como su capacidad de predicción de las enfermedades crónicas como la diabetes tipo 2 y enfermedades cardiovasculares aterotrombóticas.

Métodos: Se utilizaron bases científicas electrónicas para selección de artículos, sin límite de año de publicación.

Resultados: El ácido siálico predice el aumento de convertirse en diabéticos tipo 2 independientemente del IMC. Por otra parte, los biomarcadores α1-antitripsina, ceruloplasmina, fibrinógeno y haptoglobulina, parecen predecir el aumento de convertirse en diabético tipo 2, dependiente, de IMC. Por lo tanto, este proceso podría verse agravada por la obesidad. Las concentraciones de fibrinógeno, homocisteína y PAI-1 incrementan proporcionalmente a la insulinorresistencia, mostrando su relación con el síndrome metabólico (estado de resistencia insulínica) y con la diabetes tipo 2. En relación con las enfermedades cardiovasculares, cada biomarcador informado en esta revisión parece aumentar el riesgo, llegando a ser muy útil en el complemento pronóstico.
Introduction

The reaction of induced inflammation by factors of risk (abdominal obesity, hyperglycemia, dyslipidemias and systemic hypertension) and associated immune response are the principal events which conduct to atherogenetic process\(^1\). Individuals with these clinical manifestations, generally, show prothrombotic and pro-inflammatory states, characterized by subclinical inflammatory condition\(^2-4\), a process which could be aggravated by obesity\(^3,5,6\).

Moreover, the insulin resistance has been associated with the increase of plasmatic proteins inflammation sensitive (inflammatory biomarkers)\(^2-6\). Prospective works corroborate these associations between many inflammatory biomarkers and the diabetes and atherothrombotic cardiovascular diseases incidence\(^5,6,9\).

Hepatic Inflammation Markers

The accurate physiological events which conduct to beginning of inflammatory response in obesity are not totally known\(^11\). It is known that the mechanisms that obesity, specially central (visceral) obesity, associate with morbimortality include the increase in expression and release of adipose tissue cytokines and acute phase proteins; increase in activity of coagulation cascade (hypercoagulability) and decrease in activity of fibrinolytic cascade (pro-thrombotic process); increase in inflammatory process, oxidative stress and endothelial disfunction, besides disturbance of glucose and lipid metabolism (insulin resistance)\(^10\).

The adipose tissue has endocrine functions. Additionally, it has been proposed that pro-inflammatory cytokines formed on it, increase the hepatic synthesis of acute phase protein\(^10,11\). However, it remains unknown how the inflammation of low intensity contributes to increase risk for cardiovascular diseases in overweight and obese individuals\(^2\). This risk could be very different for individuals with similar body mass. In fact, studies show that cardiovascular risk between obese individuals vary depending on the levels of others risk factors associated with obesity\(^13,14\).

This review approaches the relation between adiposity and hepatic inflammatory markers. Moreover, it congregates the knowledge relating to possible interactions of these inflammatory mediators with chronic diseases associated to obesity, as well as, demonstrates the capacity of them in predict the risk for diabetes and cardiovascular affections.

Methods

This review was conducted using electronic scientific databases, including Medline, PubMed and SciELO, using the following key words in English, Spanish and Portuguese: inflammation, obesity, cardiovascular diseases, type-2 diabetes, sialic acid, α\(^1\)-antitrypsin and the C-terminal fragment of alpha1-antitrypsin, ceruloplasmin, fibrinogen, haptoglobin, homocystein and plasminogen activator inhibitor-1. The articles were selected after reading the abstract and regardless of their year publication.

Conclusion:

This review integrates the knowledge concerning the possible interactions of inflammatory mediators, in isolation or in conjunction, with obesity and chronic diseases, since these biomarkers play different functions and follow diverse biochemical routes in human body metabolism.

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Key words: Obesity. Insulin resistance. Inflammation. Diabetes. Cardiovascular diseases.
The adipocines (resistin, leptin and adiponectin), which are secreted by adipocytes, can also affect the inflammation and insulin resistance. As part of chronic and low intensity inflammatory process, chemokines locally secreted attract pro-inflammatory macrophages for adipose tissue, which form a crown shape structure around the dead and/or sick big adipocites. Following, these macrophages stimulate the cytokines release, which will activate the inflammatory way in adipocytes and adjacent tissues (autocrine and paracrine effect), aggravating the inflammation and insulin resistance4,10,11.

The hepatic inflammation can occur in obesity, because the activation of inflammatory pathways could be a steatosis result and/or increase in responses of hepatocytes stress pathways, which could result in hepatocytes autonomic inflammation (autocrine effect). The Kupffer cells (hepatic cells similar to macrophages) can also become activated, locally stimulating the cytokines release, which aggravated more the hepatic inflammation and insulin resistance. Moreover, the caloric excess and obesity are, frequently, come along with the increase on tissue and teidalzul free fatty acids (FFA). They could activate directly the pro-inflammatory responses in vascular endothelial cells, adipocytes, myeloid derived cells10,11. The systemic inflammation development is the result of these physiological events induced by obesity11.

Amongst the hepatic biomarkers of inflammation related to the atherosclerose process are: sialic acid, α₁-antitrypsin and the C-terminal fragment of alpha1-antitrypsin, ceruloplasmin, fibrinogen, haptogloblin, homoyctein and plasminogen activator inhibitor-1 (Fig. 1).

Sialic acid

The sialic acid or N-acetylneuraminic is component of some acute phase protein terminal part, as alpha1- antichemotrypisin, alpha1-antitrypsin, haptogloblin and orosomucoid. These glucoproteins together explain 70% of sialic acid plasmatic concentration16. Its production in hepatocytes is stimulated in inflammation and metabolic/oxidative stress situations. It could be considered a biomarker of serum concentration of many acute phase protein, beyound, could be considered a systemic inflammatory biomarker since predict the risk for type 2 diabetes and cardiovascular diseases3-16.

Non-diabetic normotensive obese individuals present the sialic acid concentration significantly increased as compared to non-obese controls. The sialic acid correlates positively with Homeostatic Model Assessment- Insulin Resistance formula (HOMA-IR), body mass index (BMI), waist and hip circumference and, negatively with Quantitative Insulin Check index (QUICKI) and insulinic sensitivity index (SI)17. Yet, the sialic acid correlate to the following measurements of adiposity and /or metabolic syndrome components: glycemia, triacylglycerol, HDL-cholesterol, systolic and diastolic arterial pressure, besides it correlates with body weight, insulin, total cholesterol and LDL-cholesterol. In this same study, how much bigger the number of metabolic syndrome components, bigger was the sialic acid concentration. For each 0.34 mmol/L of increase in sialic acid concentration, a OR for metabolic syndrome was 2.5 (1.8 to 3.4), and persisted significant after the adjustment to BMI, with OR of 1.9 (1.3 ato 2.6)11,19. In ARIC Study, individuals with the sialic acid and orosomucoid concentration bigger than average, showed odds ratio (OR) of 3.7 (1.4 to 9.8) e 7.9 (2.6 to 23.7), respectively, to develop type 2 diabetes. When adjusted for BMI and waist-hip index, the association of sialic acid and orosomucoid kept significant, with OR of 2.8 (1.01 to 8.1) and
Moreover, serum concentrations of sialic acid correlated to leptin concentrations, suggesting that high sialic acid concentration are related to biomarkers of obesity and adipose tissue metabolism, which could justify the fact of high concentrations of sialic acid precede the development of type 2 diabetes and could also explain its function as cardiovascular risk indicator.

Then, the sialic acid correlate to adiposity measurement and/or metabolic syndrome components, besides predict the increase of the risk to develop metabolic syndrome and type 2 diabetes, independently on BMI; as well as the increase of the risk to cardiovascular mortality. So, in individuals with elevation of its serum concentration, the sialic acid could add prognostic information that could be useful about obesity and chronic diseases.

Alpha1-Antitripsin and the C-terminal fragment of alpha1-antitrypsin

The α1-antitripsin is the main inhibitory endogenous human plasm proteases with serin which present a big variety of anti-inflammatory propriety, besides to execute an important function in reducing the proteolytic damage in the tissues. It is an acute phase protein and its concentration increases quickly in response to metabolic/oxidative stress due to infection and inflammation.

Even its production be mainly hepatic, some cells of immune system (neutrophils, monocytes, macrophages) also express it in response to one variety of inflammatory mediators. Some studies in vitro showed that alpha1-antitripsin inhibit the TNF-β e da IL-1 synthesis and release, however it helps the inflammatory cytokines release, as IL-10 in human monocytes. Additionally, alpa1-antitrypsin is related to atherogenic process due to its union to LDL-cholesterol receptors and carriers receptors as the CD-36, which recognize the oxidate LDL-cholesterol and mediate the accumulation of lipid and foam cells formation. The result of this interaction is the pro-inflammatory molecules production by activated monocytes.

The C-36 carboxiterminal fragment, a product of alpha1-antitrypsin degradation, is found in atheroma and related to inflammatory transcription factors, as activation of NF-kβ, PPAR-α e PPAR-γ in primary cultivation of human monocytes. Moreover, the C-36 modulates the human monocyte activation, actuating the TNF-α, IL-1β, IL-8 and the NF-kβ nuclear factor. Then, alpha1-antitrypsin, as well as, the C-36 executes a very important function on expression of regulation and on modulation of pro-inflammatory and anti-inflammatory mediator.

In ARIC Study, individual with alpha1-antitrypsin concentration bigger than average, showed an OR of 1.8 (1.6 to 4.9) to develop type 2 diabetes in the first 3 years of following, after adjustments including smoking, glycemia in fasting, BMI and waist-hip index.

Nowadays, it is necessary more information about alpha1-antitrypsin and C-36 in relation to obesity. Nevertheless, it was published that elevated concentrations of sensitive proteins to inflammation, as alpha1-antitrypsin, could predict future gain of weight.

Then, alpha1-antitrypsin executes a relevant function on expression regulation, as well as, on modulation of pro-inflammatory and anti-inflammatory mediators. Additionally, it seems to predict the increased chance to develop type 2 diabetes, irrespective of some conventional risk factors and dependently of BMI; as well as the increased risk to cardiovascular diseases. At last, individuals with elevation of alpha1-antitrypsin concentration could be come along with the inflammatory process, and high risk to develop chronic diseases, which could be aggravated by obesity.

Ceruloplasmin

The ceruloplasmin is a glucoprotein which is a family member of inflammatory sensitive protein, that include the alpha1-antitrypsin, haptoglobin, orosomucoid and fibrinogen. It is considered the main copper transporter plasmatic protein (95%) for containing 6 copper atoms per molecule. It is syntetized, mainly, by liver, but other cells (monocytes, astrocytes, Sertoli cells) can also express it. Its syntesis is increased in infection, inflammation and associated diseases situations and its concentrations could be associated to cardiovascular risk factors, as hypertension, dyslipidemias, diabetes and increase in body weight.

Besides its transport function, ceruloplasmin exerts ferrodoxase activity, modulation function of coagulation, angiogenesis, inactivity of biogenic amines and defense to oxidative stress. Due to its ferrodoxase activity, the cerulolasmin relates to iron metabolism, since catalyzes the oxidation of ferrous to ferric iron. This activity is proposal as the mechanism in which the ceruloplasmin present antioxidant effect, reducing the oxidative stress through of inhibition of Fenton reaction, which uses the ferrous iron to generates reactive oxygen species (ROS).
Otherwise, many researches have proposed a pro-oxidant effect\textsuperscript{28}. The abdominal/visceral obesity, also relates to high ceruloplasmin concentration, postulating that the determination of this protein in patient with central obesity could be useful in order to identify patients with high risk to acute myocardial infarction (AMI)\textsuperscript{29}. In other study, individuals with ceruloplasmin concentrations in bigger quartile showed RR of 2.1 (1.6 to 2.6), 2.0 (1.4 to 3.0) e 2.2 (1.6 to 3.1) for cardiac events, heart failure and cardiovascular mortality, respectively\textsuperscript{6}.

So that, high ceruloplasmin and copper concentrations associate with glucose tolerance and diabetes\textsuperscript{30}, as well as it is an important factor of cardiovascular risk when associated with homocistein concentrations\textsuperscript{31}. In a study, men with ceruloplasmin concentrations in bigger quartile when compared with smaller quartiles, the OR for type 2 diabetes increases (OR= 4.2; 6.7; 18.4), in accordance to BMI increase (IMC= <25.0; 25 a 29.9; ≥30), respectively\textsuperscript{6}.

The suggested mechanism that ceruloplasmin could contribute to development of these diseases is related to situations which disfavour the oxidative stress promoting the copper release of the ceruloplasmine molecule and then, allowing the reaction of free copper with pro-oxidants factors, which generate the free radical. Moreover, the enzymes activity in which the copper is a good cofactor (example: with the superoxide dismutase), will be prejudiced and the same way, the ferroxidase activity that depend on the molecule integrity, modifying the iron metabolism and favoring its accumulation\textsuperscript{32}.

So, high ceruloplasmin concentrations predict the increased of the risk to develop cardiovascular diseases, as well as, the increase of the chance to present type 2 diabetes, irrespective of BMI. But, it is important to stand out that high concentrations could not be pathologic, necessarily.

In clinical practice, the best way to know it, is understand the oxidative degree, and then, determine IF this elevation is pathologic\textsuperscript{37}. Anyway, the ceruloplasmin could be pro-oxidant or antioxidant effect, depending on the integrity of its structure. The ceruloplasmin functions in stress oxidative situations and as biomarker of inflammatory state request new investigations\textsuperscript{3}.

**Fibrinogen**

The fibrinogen (Factor I) is a glucoprotein synthesized in the liver and is involved in final stage of coagulation, which consists on its conversion in fibrin under trombin action\textsuperscript{14}. It is an acute phase protein, similar to C-reactive protein (CRP), its production is apparently controlled by IL-6\textsuperscript{38}. The fibrinogen promotes the arterial and venous thrombosis through of increase in fibrin formation, plaquetry aggregation and plasma viscosity, promoting the atherosclerosis by proliferations of endothelial and smooth vascular muscle cells\textsuperscript{39}.

Since the obesity is associated with atherosclerosis, many researches have been conducted in order to know possible associations between the fibrinogen and obesity and its comorbidities. In individual without diabetes, the fibrinogen concentration correlated to following adiposity measurement and/or metabolic syndrome components: fasting glycemia, waist circumference, HDL-cholesterol, systolic and diastolic arterial pressure, besides BMI, insulin, pro-insulin values and S\textsuperscript{3}\textsuperscript{3}. Additionally, overweight individuals have higher fibrinogen concentration when compared to normal\textsuperscript{34}; and individuals with metabolic syndrome have fibrinogen concentrations significantly bigger than individual without metabolic syndrome\textsuperscript{35}. Otherwise, fibrinogen concentrations could decrease in weight loss\textsuperscript{36}.

A study showed positive correlation between concentrations of insulin and fibrinogen, during many periods of glucose tolerance (normal tolerance, prejudiced tolerance to glucose and type 2 diabetes, respectively). The decrease of insulin sensitivity was an independent factor associated with high fibrinogen concentrations\textsuperscript{37}. These results suggest that fibrinogen is a metabolic syndrome biomarker, in an insulin resistance state. In ARIC Study, individuals with fibrinogen concentrations in the bigger quartile, showed OR of 1.2 (1.0 to 5.0) to develop type 2 diabetes in a period of 7 years\textsuperscript{1}. In other study, men with fibrinogen concentrations in the major quartile when compared with the smaller quartiles, the OR to type 2 diabetes increases (OR= 4.2; 7.8; 21.6), in accordance to the BMI increase (BMI = <25.0; 25 a 29.9; ≥30), respectively\textsuperscript{6}.

In relation to cardiovascular diseases, individuals with fibrinogen concentration in major quartile showed a RR of 2.3 (1.8 to 2.9), 1.9 (1.3 to 2.7) e 2.5 (1.8 to 3.4) to cardiac events, heart failure and cardiovascular mortality, respectively\textsuperscript{6}. In a prospective cohort study, each increase of 100md/dl of fibrinogen level yielded a hazard ratio (HR) of 1.49 (1.11 to 2.22) for cardiovascular mortality, after adjusting for sex, age, hypertension, diabetes mellitus, obesity, total cholesterol, HDL-cholesterol/triacylglycerols ratio, smoking habit, and history of previous cardiovascular disease. Within the population of this study, fibrinogen is an independent predictor of cardiovascular mortality\textsuperscript{38}.

Fibrinogen concentrations also predict weight gain. It was demonstrated by a study in which individuals with serum concentrations of fibrinogen in higher quartile, acquired approximately 0.23 kg/year when compared to them of smaller quartiles. The OR adjusted for the biggest weight gain (bigger than percentil 90) for that in the bigger quartile of fibrinogen concentration was de 1.65 (1.38 – 1.97) times when compared with them in the smaller quartile, for a period of 3 years. These OR values were also different for distinct degrees of obesity. Individuals with BMI < 25, 25 to 30 e > 30 kg/m\textsuperscript{2} have their OR of 1.43, 1.59 e 2.02, respectively\textsuperscript{39}. Then, high fibrinogen concentrations predispose the obese patients to higher risk to suffer thromboembolic complications\textsuperscript{40}, due to increa-
se on oxidative and inflammatory state, favoured by increase in body adiposity.

The fibrinogen correlate to adiposity measurement and/or metabolic syndrome components and its concentrations increase proportionally to insulin resistance state, increasing the chance to occur type 2 diabetes, which happen in dependent way of BMI. So, in clinical practice, the same could add useful prognostic information to individuals with metabolic syndrome, an aggravated process by obesity, which predispose individuals to tromboembolic diseases. At last, there is an additional advantage associated with the determination of fibrinogen concentration, since it is considered an independent very important risk factor to cardiovascular diseases.

Haptoglobin

The haptoglobin (α-1-globulin) is a glucoprotein produced, mainly, in the hepatocytes, whose function principal is to fix the free hemoglobin and remove it of circulation by the reticuloendothelial system. As an acute phase protein, its synthesis is increased in inflammatory process. Besides its hepatic synthesis, it has been demonstrated its presence in adipose tissue, as well as its release by primary cultivation. Its quantity is major in visceral than subcutaneous tissue, but in both cases are much inferior than circulating concentrations. Amongst the cytokines, TNF-α, IL-6 and others, regulate its secretion in the liver and adipose tissue.

In healthy individuals, the haptoglobin concentration correlate to following adipose measurements and/or metabolic syndrome: insulin, total cholesterol, percentual of body fat, lipid oxidation, leptin, CRP and/or metabolic syndrome. The relation power between hyperhomocysteinemia and haptoglobin concentration bigger than average, showed an OR of 2.1 (0.7 to 6.0) to develop type 2 diabetes in 3 first years of following, after the adjustment including smoking, fasting glycemia, BMI and waist-hit index. In other study, men with Hp concentration in the major quartile when compared to smaller quartiles, the OR to type 2 increase (OR= 3.2; 8.4; 21.6), accordant to BMI increase (BMI> 25.0; 25 a 29.9; ≥30), respectively. In ARIC Study, individuals with haptoglobin concentration bigger than average, showed an OR of 2.1 (0.7 to 6.0) to develop type 2 diabetes in 3 first years of following, after the adjustment including smoking, fasting glycemia, BMI and waist-hit index. In other study, men with Hp concentration in the major quartile when compared to smaller quartiles, the OR to type 2 increase (OR= 3.2; 8.4; 21.6), accordant to BMI increase (BMI> 25.0; 25 a 29.9; ≥30), respectively.

In relation to cardiovascular diseases, individuals with haptoglobin concentration in bigger quartile showed an RR of 2.0 (1.6 to 2.5), 1.9 (1.3 to 2.7) and 2.0 (1.5 to 2.7) for cardiac events, acute myocardial infarction and cardiovascular mortality, respectively. Despite the found association between haptoglobin concentration and adipose measurement and/or components of metabolic syndrome, as well as its capacity to predict the risk to type 2 diabetes, dependently of BMI, and to cardiovascular diseases, its use as marker of inflammatory state in clinical and epidemiologic researches should be done and elucidated with caution, due to different behaviour showed by its 3 main phenotypes (haptoglobulin1-1; haptoglobulin1-2 e haptoglobulin 2-2).

Homocysteine

The homocysteine is an aminoacid which contain a thiol (sulphidril or SH-) that exerts an important function in folate and methionine metabolism. The homocysteine is metabolized by two pathways: (a) when the metionin stock is sufficient, the homocysteine enter on transulfuration pathway and is converted in cistein in one reaction catalyzed by β-sintase cistationin dependent on B6 vitamin; (b) when the metionin conservation is necessary, the homocysteine receive a methyl group of N5 methyl-tetrahydrofolate (catalyzed by N5, N10 methylentetrahydrofolate reductase enzime) and is converted to metionin by methionine synthase (demethylation), whose cofactor in this last reaction is the B12 vitamin.

The hyperhomocysteinemia was, recently, recognized as a factor of cardiovascular risk, independent on others risk factors as diabets, hypertension, hypercholesterolomea and smoking. The estimated prevalence to hyperhomocysteinemia (Hoo>16 µmol/L) vary between 5% and 30% in population, and occur in approximately 5 to 7% of population in generaly, and in 5 to 40% in patients with cardiovascular diseases.

In a populational study, HOOGEVEN et al., (2000) detected a prevalence of 25.8%. The relation power between hyperhomocysteinemia and death seems to be stronger between individuals with diabetes than that one’s without this disturb. In fact, an interaction of hypercysteinemia with diabetes is biologically plausible. High homocystein concentrations could exert atherothrombotic effects by oxidative stress increase, which could induce endothelial disfunction. The homocysteine can also affect the propriety of extracellular matrix and increase the smooth muscle cells proliferation. In diabetes, the oxidative stress is enhanced, and extracellular matrix alterations are poeninent features of diabetes. The both could become individuals with diabetes more susceptible to adverse effects of hyperhomocysteinemia. Additionally, the oxidative stress caused by the increased concentration of triaciglycerols and free fat acids is known in to cause the hyperinsulinemia and insulin resistance. This process could be aggravated in obesity in decurrency of the stock increase of body fat. The process is bidirectional and the insulin resistance could enhance the homocysteine concentration.

However, the specific mechanism through the homocysteine promote atherothrombotic continuous unknown, there are strong epidemiological evidences to association between hyperhomocysteinemia and atherothrombotic cardiovascular diseases. Otherwise, as was showed by meta-analysis studies, the daily treat-
ment with pholic acid could reduce the homocysteine concentration in 15 up to 40% into 6 weeks47. Then, the hyperhomocysteinemia is an important risk factor but could be modified by diet habit.

In a prospective study, after the adjustment to the biggest cardiovascular risk factors, the serum albumin (marker of healthy general state) and glycated hemoglobin (HbA1c), the OR to mortality into 5 years was 1.56 (1.07 to 2.30) to hyperhomocysteinemia and 1.26 (1.02 to 1.55) for each 5-µmol/L of homocysteine increase. Moreover, the OR pto mortality in 5 years to hyperhomocysteinemia was 1.34 (0.87 to 2.06) in individuals without diabetes and 2.51 (1.07 to 5.91) in diabetics (p<0.08). For each 5-µmol/L of serum homocystein increment, the risk to general mortality in diabetics (p<0.08). For each 5-µmol/L of homocysteine in 5 years increase in 17% patients without diabetes and 60% in diabetics50. In other study, how much big was the quartile of homocystein concentration (Q1: <10.3; Q2: 10.3-12.49; Q3: 12.5-15.39; Q4: >15.4), bigger was the OR adjustment to heart failure, wich were 1.0, 1.2 (0.3 to 4.2), 2.6 (0.7 to 9.3) and 4.7 (1.1 to 20.0), respectively48.

Then, the hyperhomocysteinemia is related to morbimortality of independent form of biggest cardiovascular risk factors45,50 and seems to be a strong risk factor (about 2 times) to death in diabetics50, which process could be aggravated in hyperinsulinemias45. So, in individuals with its high concentrations, the homocystein per se could be useful in clinical practice to supply prognostic in relation to chronic diseases. Still, is important to stand out that the risk to chronic diseases, followed by the increase in homocysteine concentration, could be modified by diet habit.

Plasminogen activator inhibitor-1

The PAI-1 is a protein that inhibits the tecidual plasminogen activator (tPA), which cleaves the plamine to plasminogen, thus is the first physiological inhibitor of fibrinolysis in vivo. It occurs while present the capacity to inhibit the plamine forerunner, whose function is the rupture of fibrine network, avoiding the thrombus formation51. The PAI-1 is produced in many tissues, including the liver and adipocytes. Many factors contribute to increase of the expression and release of PAI-1 in adipose tissue (specially, the visceral), amongst them there are insulin, TGF-β, PCR, IL-6, FNT-α and IL-1β,54. These factors associated with the stock increase of body fat can explain theirs enhanced concentration, generally, verified in obese individuals and/or insulin resistant55.

These high concentration compromise the normal fibrine clearance, causing the fibrinolysis system deterioration, and consequently promote the thrombose, which is part of cardiovascular complication of obesity53.

The PAI-1 concentration correlates to following adiposity measurements and/or metabolic syndrome components: waist circumference, insulin resistance and triacylglycerols concentrations. High concentration of PAI-1 predicts cardiac and coronary diseases and acute myocardial infarction. Then, high concentrations of PAI-1 found in obesity and metabolic syndrome could predispose to many micro and macrovasculars, arterials and venous, including the thrombose51.

A study demonstrated positive correlation between insulin and PAI-1 concentration, during many periods of glucose tolerance (normal, prejudiced tolerance to glucose and type 2 diabetes), respectively. The decrease sensitivity to insulin was an independent factor associated with high PAI-1 concentrations57.

The IRAS Study evaluated the link between PAI-1 and the incidence of type2 diabetes during 5 years and observed that PAI-1, which has a knowed relation to metabolic syndrome components, it seems to be a precocious inflammatory biomarker to type2 diabetes. The PAI-1 concentrations are enhanced in insulin resistant individuals, who become diabetics independently on insulin sensitivity and BMI5. These results suggest that PAI-1 is a metabolic syndrome marker, in insulin resistance state, due to reflect subclinical inflammation.

The PAI-1 activity could be stimulated by others inflammatory mediators, as the PCR which stimulate the expression and PAI activity in endothelial cells. This effect is additional in hyperglicemia situation. So, the increase of PAI-1 concentration on diabetes and metabolic syndrome, is also due to a stimulation of monocytes and endothelial cells by PCR, in which situations are also increased55,56.

A study with elders without diabetic, after to adjust the age, the PAI-1 concentrations correlated to following adiposity measurements and/or metabolic syndrome components: waist circumference, glycemia, HDL-cholesterol, body weight and insulin. In this study, the authors also related the PAI-1 concentration to body mass factors (body weight, waist circumference, insulin and glycemia). Then, individuals with high concentrations of PAI-1 together with body mass factor support the relation between obesity and prejudiced fibrinolysis57.

Obeses with metabolic syndrome have higher PAI-1 concentrations than individuals with normal weight without metabolic syndrome55. Additionally, in the same study, the PAI-1 concentration to whole group (obese with metabolic syndrome plus eutrofics) were associated with glycemia, insulin, HOMA-IR, triaciylglycerol, HDL-cholesterol and CRP. Only in obese group with metabolic syndrome, the PAI-1 concentration was significantly associated with glycemia and HOMA-IR. So, the high serum concentrations of PAI-1 are found in obeses with metabolic syndrome, but these are dependents factors of others conditions for that inflammatory process occur. The association between PAI-1 and insulin resistance has been reported by many studies with eutrofics patients and obeses with insulin resistance45.
Then, the determination of PAI-1 concentration has the advantage to be related to adiposity measurement and/or metabolic syndrome components and the fibrinolysis system. This parameter is also considered an important risk factor to type 2 diabetes and to atherothrombotic cardiovascular diseases, aggravated by insulin resistance degree.

**Inflammatory biomarkers set (fibrinogen, haptoglobulin, ceruloplasmine, orosomucoid, α-antitripsin)**

In a study, the OR to type 2 diabetes in men with high concentrations of biggest quartile for no biomarker (OR= 3.3; 3.8; 13.9), presence of one (OR= 4.0; 6.3; 12.8), for two (OR= 3.3; 6.7; 20.8), for three (OR= 5.4; 6.9; 16.9) e for four or five (OR= 2.5; 8.7; 28.0), when compared to smallest quartiles, increased with BMI (BMI= <25.0; 25 to 29.9; ≥30), respectively. The prevalence of diabetes was significantly associated with studied biomarkers concentrations among overweight and obese individuals, but not in individuals with BMI <25 kg/m². This association was similar to insulin resistance in accordance to HOMA-IR.{ref}

In this same study, individuals with and without diabetes, as well as the presence of two up to five biomarkers on fourth quartile, when compared to lowest quartiles, had different OR to atherothrombotic cardiovascular diseases. After adjusted to age, smoking, cholesterol, triacylglycerols, sedentary life, systolic and diastolic arterial pressure and hypertension medications; men without diabetes, with two up to five biomarkers had OR of 1.6 (1.4 to 1.8); 1.7 (1.4 to 2.2); 1.6 (1.3 to 1.9); 1.4 (1.1 to 1.9) and 1.4 (1.0 to 1.9) for every cardiovascular mortality causes (cardiovascular diseases, cardiac events, infarct, ischemic infarct, respectively). And men with diabetes and presence of two up to five biomarkers had possuíam OR of 1.5 (0.93 to 2.4); 2.2 (1.2 to 4.2); 2.2 (1.2 to 3.8); 2.4 (0.98 to 5.8) and 2.0 (0.8 to 5.0) for all cardiovascular mortality causes (cardiovascular diseases, cardiac events, infarct, ischemic infarct, respectively). The authors concluded that on this study population (6,050 men), the diabetes was associated with the increase of inflammatory biomarkers concentrations (fibrinogen, haptoglobulin, ceruloplasmine, orosomucoid, α-antitripsin) between individuals with overweight and obesity, but not between individuals with normal weight. Additionally, high concentrations of inflammatory biomarkers increase the cardiovascular risk similarly in diabetics when compared to individuals without diabetes{ref}.

**Final Considerations**

This review allows to verify the relation between some biomarkers (sialic acid, fibrinogen, haptoglobin and PAI-1) with obesity and chronic diseases, since them presented correlation to adiposity measurements and/or metabolic syndrome components. The sialic acid predicts the chance increase to become type 2 diabetic independently of BMI. Moreover, the α-antitripsin, ceruloplasmine, fibrinogen and haptoglobulin biomarkers, seem predict the chance increase to become type 2 diabetic, dependently, of BMI. So, this process could be aggragated by obesity. The concentrations of fibrinogen, homocystein and PAI-1 increase proportionally to insulin resistance, showing its relation to metabolic syndrome (insulin resistance state) and with type 2 diabetes.

In relation to cardiovascular diseases, every biomarkers reported in this review seem to increase the risk, becoming useful in add important prognostic. It seems that fibrinogen and homocystein, in specially, have an additional advantage in its use in clinical practice, because they are considered independent risk factors to cardiovascular diseases.

The high concentration of ceruloplamin, should be interpreted with caution, because could be not necessarily pathologic. In the clinical practice, the best way to confirm this situation is to evaluating the oxidative state. In any way, the ceruloplasmin function of inflammatory biomarker in oxidative stress situation request new investigations.

It is important to stand out that the strong relation between inflammation biomarkers and chronic diseases could be equal as much in healthy as in sick individuals (after have been developed type 2 diabetes or had myocardial infarction), as well as in eutrofic and overweight individuals. In the same way, the cardiovascular risk varies widely between eutrofic and overweight individuals, with low or high concentrations of inflammatory biomarkers. Their relation to sensitive protein to inflammation contributes, but do not explain completely in increase of cardiovascular risk in obeses. It suggest that the contribution of insulin resistance on inflammatory process in not only a phenomenon restricted to individual with diseases or overweight. All factors which modulate the liver and adipose tissue to product inflammatory biomarkers should be more explored; however, there is an inability in find differences on inflammatory biomarkers concentrations between healthy and sick individuals, and between eutrofic and overweight individuals.

An context, specially on food patterns and physical activity, should be considered into determinants of chronic diseases and not only in biochemistry and anthropometric values, and body composition.

The inflammatory process is a very complex reaction. All of these reported biomarkers, alone or together, seem execute many functions and following various biochemistry routs in human body metabolism. At last, is necessary performing more studies to understand better the biological activity of these inflammatory biomarkers, and then, stablish their biological and clinical function.
References


