Chapter 6 Pro-inflammatory cytokines: leptin and visfatin associated to obesity in young university students

Capítulo 6 Citocinas pro-inflamatorias: leptina y visfatina asociadas a obesidad en jóvenes universitarios

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Abstract

Obesity has been associated with the development of important degenerative diseases such as hypertension, metabolic syndrome, diabetes mellitus (DM), cardiovascular disease (CVD), cancer, among others. And is also described that the disease severity of infections illnesses such as coronavirus, influenza, parainfluenza, and rhinovirus in increased. Besides, in 2009 was recognized as a risk factor during the pandemic of influenza H1N1 Currently there are several studies which suggest that some adipocytokines as leptin, resistin, plasminogen activator inhibitor-1 (PAI-1), adiponectin, visfatina among others have mediators affects in cardiovascular system.

Some authors had shown plasmatic levels of leptin seem to be one of the best biological markers of obesity, and hyperleptinemia is closely related with several metabolic risk factors on insulin resistance in DM Some studies reveals that visfatin have mimetic affects with insulin in muscle stimulation and in glucose transport in adipocyte, also inhibit glucose production in liver. The objective of this work was to describe the association between leptin and visfatina in the development of obesity in a young population to identify the possible risk factor or as a protective factor of this adipocytokines with obesity.

Methodology. Cross-sectional study. The present study was carried out in the facilities of the Centro Universitario de Ciencias Exactas e Ingenierías of the Universidad de Guadalajara. We recruit 171 young students (57.6 % female, 42.4% male) with the following characteristics: age between 18- 25 years old, fasting of 8 to 10 hours to take the blood sample.

The results shows that BMI is higher in male and triglycerides also. On the other hand, leptin levels and total cholesterol are higher in women. The group with hyperleptinemia has higher values of BMI, total cholesterol, triglycerides, LDL and visfatina comparing with the group with normal leptin levels.

We observed that hyperleptinemia is a risk factor for the development of obesity with OR 5.86 (p=0.01), in the other hand, visfatina acts as a protector factor with OR 0.2901 (0.02).

Conclusion. Therapeutic intervention in early stages previous the beginning of the metabolic complications could have a favorable cost-benefit. However, the incorporation of markers such as the size of the particle of LDL, insulin resistance index, adipocytokines pro inflammatory as leptin and visfatin could improve the current predictive capacity.

Obesity, Leptin, Leptin, Visfatin, Young people, Proinflammatory

Resumen

La obesidad se ha asociado al desarrollo de importantes enfermedades degenerativas como la hipertensión, el síndrome metabólico, la diabetes mellitus (DM), las enfermedades cardiovasculares (ECV) y el cáncer, entre otras. Y también se describe que la gravedad de las enfermedades infecciosas como el coronavirus, la gripe, la parainfluenza y el rinovirus en aumentada. Además, en 2009 se reconoció como un factor de riesgo durante la pandemia de gripe H1N1 Actualmente hay varios estudios que sugieren que algunas adipocitoquinas como la leptina, la resistina, el inhibidor del activador del plasminógeno-1 (PAI-1), la adiponectina, la visfatina entre otros tienen efectos mediadores en el sistema cardiovascular.

Algunos autores han demostrado que los niveles plasmáticos de leptina parecen ser uno de los mejores marcadores biológicos de la obesidad, y que la hiperleptinemia está estrechamente relacionada con varios factores de riesgo metabólico en la resistencia a la insulina en la DM. Algunos estudios revelan que la visfatina tiene efectos miméticos con la insulina en la estimulación muscular y en el transporte de glucosa en el adipocito, además de inhibir la producción de glucosa en el hígado.

El objetivo de este trabajo fue describir la asociación entre la leptina y la visfatina en el desarrollo de la obesidad en una población joven para identificar el posible factor de riesgo o como factor protector de esta adipocitoquina con la obesidad.

Metodología. Estudio transversal. El presente estudio se realizó en las instalaciones del Centro Universitario de Ciencias Exactas e Ingenierías de la Universidad de Guadalajara. Reclutamos a 171 jóvenes estudiantes (57.6 % mujeres, 42.4% hombres) con las siguientes características: edad entre 18-25 años, ayuno de 8 a 10 horas para tomar la muestra de sangre.

Los resultados muestran que el IMC es mayor en los hombres y también los triglicéridos. Por otro lado, los niveles de leptina y el colesterol total son mayores en las mujeres. El grupo con hiperleptinemia tiene valores más altos de IMC, colesterol total, triglicéridos, LDL y visfatina en comparación con el grupo con niveles normales de leptina. Observamos que la hiperleptinemia es un factor de riesgo para el desarrollo de la obesidad con OR 5,86 (p=0,01), en cambio, la visfatina actúa como factor protector con OR 0,2901 (0,02).

Conclusión. La intervención terapéutica en estadios tempranos previos al inicio de las complicaciones metabólicas podría tener un coste-beneficio favorable. Sin embargo, la incorporación de marcadores como el tamaño de la partícula de LDL, índice de resistencia a la insulina, adipocitoquinas pro inflamatorias como la leptina y la visfatina podría mejorar la capacidad predictiva actual.

Obesidad, Leptina, Visfatina, Jóvenes, Proinflamatorio

6.1 Introduction

At present, obesity is considered by the World Health Organization to be one of the most serious health problems in the world. (OMS) and other organizations as a worldwide epidemic. (Collaboration NCDRF, 2016) It is a disorder characterized by a disproportionate increase in body weight in relation to height mainly due to fat accumulation. Several factors influence the development of this disease: genetic, environmental and behavioral are the main ones (Bray *et al*, 2018). Usually the criterion used for diagnosis is the body mass index. (IMC), where a value between 25-29.9 Kg/m^2 as overweight and a value equal to or greater than 30 Kg/m^2 as obesity. (Rangel-Huerta *et al,* 2019)

Epidemiologically, obesity has undergone a significant increase in recent decades. According to data from the OMS, has tripled in prevalence since 1975. As of 2016, 1.9 billion (39% of the world's population) adults were estimated to be overweight, of which about 650 million are obese. (WHO, 2018). In Mexico, the prevalence of overweight and obesity reported in the National Nutrition Survey 2018 was 76.8% in women and 73% in men. Likewise in young university population values of 32.7% have been reported. (INSP 2018; González *et al,* 2014)

It has been associated with the development of important chronic degenerative diseases such as: hypertension, metabolic syndrome, diabetes mellitus (DM), cardiovascular diseases (CVD), cancer among others. (Williams et al, 2015) And it has been described to be associated with increased severity of infectious diseases such as coronavirus, influenza, para influenza and rhinovirus.

In addition, in 2009 it was recognized as an independent risk factor in the pandemic caused by the influenza A, H1N1 variant (Kwok et al, 2020). (Kwok et al, 2020) On the other hand, in the current COVID19 pandemic, several studies have shown that the risk of severe disease is increased in the presence of obesity, as well as the rate of hospitalization and a negative outcome. (Druncker D.J., 2021)

The relationship between obesity and these various pathologies has been described mainly due to the increase in adipose tissue, since this is associated with an increase in metabolic activity, which leads to inflammation, greater risk of thrombosis and alterations in carbohydrate metabolism. Its metabolic products, called adipokines, play an important role in energy homeostasis, carbohydrate and lipid metabolism, intake control, thermogenesis, cell viability, reproduction, immunity, neuroendocrine function, and the structure and function of the cardiovascular system. (Choe et al, 2016)

Currently, several studies suggest that the levels of some adipocytokines such as leptin, resistin, plasminogen activator inhibitor-1 (PAI-1), adiponectin, visfatin, among others, mediate cardiovascular effects due to their effects on the body. These constitute a family of hormones with important actions in the cardiovascular system. (García-Torres *et al,* 2011).

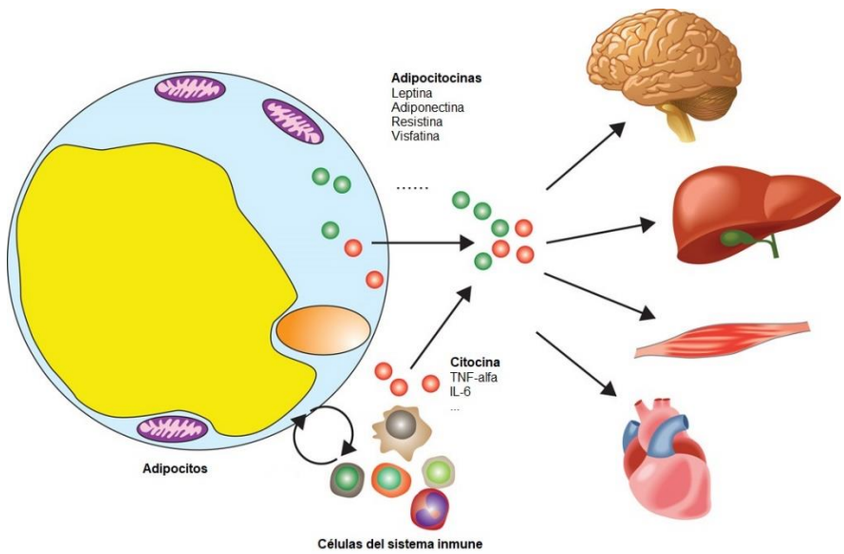
Obesity and inflammation

The first evidence of obesity-related inflammation arose from a report of elevated TNFα in adipose tissue in obesity. Since then, numerous studies have consistently demonstrated increased inflammation in adipose tissue in obese animals and humans. Although inflammation in people with obesity has been described as occurring in a variety of tissues, there is evidence that most of it occurs in adipose tissue (Wu & Ballantyne, 2020).

The mechanisms that explain the relationship between obesity and inflammation remain poorly understood; however, obesity has been considered a chronic low-grade inflammatory state that provides a direct relationship with various pathologies such as metabolic syndrome and cardiovascular disease. The final common pathway is atherosclerosis, causing generalized vascular disease, leading to arterial hypertension, coronary artery disease and peripheral vascular disease. (Aprahamian *et al*, 2011).

It has now been demonstrated that adipose tissue actively participates in immune and inflammatory processes. When excess fat is present, an "inflammatory environment" is created with the release of adipocytokines such as leptin, visfatin and resistin (Fig. 6.1), which are also believed to contribute to the development of insulin resistance. Furthermore, adipocytokines, especially leptin, activate endothelial cells and the accumulation of macrophages in adipose tissue, which release proinflammatory molecules, including TNF-α, thus perpetuating the inflammatory state described in obesity. (Hugo & Ben, 2016).

Figure 6.1 Inflammation in adipose tissue



Adipocytes in a state of inflammation characterized by obesity modify cytokine release levels and their actions are generally altered. Adipocytokines are also sent to remote organs to regulate energy metabolism.

Source: Cao H. (2014)

The adipocyte as an endocrine tissue

An indisputable protagonist in the pathophysiological process of obesity is the adipose tissue and, in particular, the adipocyte, an extremely active cell whose physiological role involves, in addition to general metabolic regulation, cell growth, immune response, thermogenesis, and reproductive and cardiovascular functions. (Nava Santana et al, 2013). Recently, white adipose tissue (WAT) has been recognized not only as an energy reservoir, but also as an important secretory organ of numerous bioactive molecules identified as important chemical messengers with local and systemic actions called adipokines. The mechanism of action of these molecules involves a great diversity of receptors and intracellular signaling cascades that act in a variety of cells -including the adipocyte- through well-defined autocrine signals and in many neighboring cells inhabiting the same adipose tissue, establishing very complex paracrine communications and participating in energy homeostasis to maintain the body metabolism in an adequate balance. (Martinez-Sanchez, 2020)

Alterations in the adipocyte induced by overeating and sedentary lifestyle and aggravated by all the factors related to increased metabolic and cardiovascular risk, are the starting point for a cascade of events leading to metabolic imbalance. In addition, the inflammatory response indicated in TAB produces a chronic situation at the systemic level that eventually leads to insulin resistance, atherosclerosis and alterations typical of MS. (Nava Santana et al, 2013).

Leptin

It is a hormone secreted by adipose tissue that plays an important role in the control of energy homeostasis, through binding to its ligand LepR which is mainly expressed in the hypothalamus. (Seoane-Collazo et al.2020) Blood leptin levels (3.9 ng/mL) reflect the amount of energy stored in adipose tissue and has been correlated with the degree of obesity. (Perez-Perez et al, 2020)

Studies have shown that plasma leptin levels appear to be one of the best biomarkers of obesity, and that hyperleptinemia is closely associated with several metabolic risk factors related to IR in DM. (Martinez-Sanchez, 2020)

There is a significant relationship between insulin and leptin, but it is not immediate. The molecule leptin has a role in the development of IR and is postulated as a link between obesity and DM. Obesity is an established risk factor for the development of DM2, affecting individuals who show signs of IR and hyperinsulinemia, although the mechanism by which DM and obesity are associated is not clear, it is argued that leptin could play a key role in this mechanism. (Seoane-Collazo et al, 2020).

Recent evidence suggests that leptin and insulin, in addition to their critical role in the regulation of energy homeostasis, may also play an important role in the hypothalamic control of glucose metabolism, with leptin being a regulator of glucose homeostasis, independently of its effects on food intake. Hyperleptinemia is common in obesity and reflects increased adiposity and leptin resistance. Notably, the renal actions of leptin may play an important role in the pathogenesis of obesity-related hypertension and MS. In addition, the lipotoxic effect of leptin resistance may cause IR and β-cell dysfunction increasing the risk of type 2 DM. (Mendez et al, 2009)

Visfatina

It is an adipocytokine secreted by adipocytes, macrophages and inflamed endothelial tissue, and is elevated in obesity, insulin resistance and DM2. This cytokine acts as a proinflammatory mediator, with the ability to induce MT1 metalloproteinase in human monocytes and endothelial cells, and therefore plays an important role in the pathogenesis of vascular inflammation produced in obesity and type 2 diabetes. (Landencho *et al*, 2019).

Also known as pre-B cell colony enhancing factor, it is highly expressed in visceral fat and was originally isolated as a secreted factor that upregulates interleukin 7 (IL-7) and the stem cell responsible for promoting the growth of B cell precursors. It has been postulated to play an important role in innate immunity. However, the biological activity of visfatin is still poorly understood. It is secreted by activated lymphocytes, monocytes and neutrophils. It stimulates the expression of Interleukin 6 (IL-6) and interleukin 8 (IL-8) in amniotic cells, and prolongs neutrophil survival in clinical sepsis. (Sheta *et al*, 2012)

Visfatin has been reported to exert insulin mimetic effects on stimulated muscle and adipocyte glucose transport and inhibit hepatocyte glucose production. It was also found to bind to and activate the insulin receptor, causing phosphorylation and activation of the signaling molecule pathway. However, visfatin and insulin do not compete for binding to insulin receptors, indicating that the two proteins are recognized in different regions of the receptor. It could be that it also plays a role in glucose homeostasis and the pathogenesis of DM. (Sheta et al, 2012)

High visfatin levels are also correlated with an increased risk of adverse cardiac events in patients with myocardial infarction and it has been observed that in addition in weight loss after bariatric surgery the levels decrease. Landencho et al, 2019). The role of this adipocytokine with respect to obesity has been entirely conclusive, as contradictory results have been found. Sheta et al in 2012 found that visfatin expression in visceral fat in obese subjects and visfatin concentrations in plasma correlated closely with the amount of visceral fat, better than subcutaneous fat. On the other hand, other work has found an inverse association between circulating visfatin levels and obesity. One study found that visfatin levels were negatively related to visceral fat tissue and triglycerides. And positively to HDL cholesterol. (Wang et al, 2007, Sheta et al, 2012)

Due to the increase of obesity in recent years and the not very encouraging prognosis of its acceleration, identifying the pathogenesis of this disease and the possible role of inflammation through the evaluation of proinflammatory adipocytokines will allow a better understanding of the pathogenesis and disorders related to this disease. Therefore, the aim of this work was to describe the association between leptin and visfatin with obesity in a young population in order to identify the possible role as a risk factor or protective factor of these in obesity.

6.2 Materials and methods

The work carried out was an analytical cross-sectional study.

The study was carried out in the facilities of the University Center of Exact Sciences and Engineering of the University of Guadalajara. An invitation was made to the general population of the university center and a total of 171 young people were obtained with the following characteristics: 18 - 25 years old, not under treatment for obesity, not taking corticoids and who presented themselves with a fasting period of 8 - 10 hours to obtain the blood sample.

Those who complied with the inclusion requirements were summoned to the laboratory in the morning and there they filled out their clinical history. Subsequently, anthropometric measurements (weight and height) were taken to calculate the body mass index (BMI), for classification into people with and without obesity. A blood sample was then obtained to determine biochemical parameters.

The parameters obtained were obtained as follows:

- Body Mass Index. The formula Weight (kg)/Height (m^2) was used to calculate the BMI. A Tanita 30A scale was used to obtain the weight and its scalimeter was used for the height.

- Determination of adipocytokines: Serum determination was performed using a sandwich ELISA technique in a Magpix Luminex kit with a Pre-Diabetes Kit. Human Assay de BioRad©.

For the identification of obesity and NON-obesity, the points established by the World Health Organization were taken into account. 18 – 29.9 Kg/m2 and as obesity for those with a BMI greater than 30 Kg/m^2. (WHO, 2018)

For the separation into people with normal and elevated leptin, the cut-off points used were normal leptin, normal leptin, elevated leptin and elevated leptin. 0- 3.9 ng/mL and hyperleptinemia > 3.9 ng/mL. And for normal visfatin 0 – 1.48 ng/mL and elevated visfatin was considered when it was greater than 1.48 ng/mL. (Wang *et al*, 2007)

In addition, biochemical parameters were analyzed for a better description of the population such as glucose and lipid profile composed of: Cholesterol, triglycerides, HDL and LDL. It was performed from a blood sample in a dry chemistry equipment. Fujifilm Drichem N500imx®; total cholesterol, HDL and triglycerides. And using the Friedewald formula, VLDL and LDL were calculated.

Statistical analysis. Descriptive statistics were performed, presenting the results as mean and standard deviation in the case of quantitative variables. As well as frequencies in the case of qualitative variables. The association between variables was carried out by means of a Chi-squared test for the calculation of Odds Ratio. A value $p < 0.05$ fue considerado como significativo. We used the Excel package and the program Graph Pad version 5 for the development of the analysis.

Ethical aspects. This study is in accordance with the General Health Law of the United Mexican States regarding research, which according to Art. 17 of the research regulations considers minimum risk research, and each volunteer signed an informed consent form. The privacy of each individual is protected and he/she has the right to withdraw at any time from the study. The work also has the approval of a bioethics committee of the work center.

6.3 Results

A total of 171 young people who met the inclusion criteria were recruited. They ranged in age from 18 - 25 years with a mean of 20.6. Of these 57.6% (n=98) were female and 42.4% (n=73) were male. Table 6.1 below shows the descriptive results of the population compared by gender.

Table 6.1 Descriptive results of the population separated by gender

Parameter	General n= 171	Women n= 98	Men n= 73
Age	20.6 ± 1.66	20.32 ± 1.38	21.00 ± 1.91
IMC (Kg/m^2)	25.8 ± 6	24.05 ± 4.98	28.11 ± 6.48
Glucose (mg/dL)	85 ± 8.31	84.61 ± 7.92	85.55 ± 8.82
Total Cholesterol (mg/dL)	168.1 ± 35.09	172.35 ± 35.22	162.34 ± 34.30
Triglycerides (mg/dL)	98.84 ± 52.27	88.40 ± 47.50	112.90 ± 55.36
HDL (mg/dL)	46.88 ±12.57	51.78 ± 12.55	40.30 ± 9.18
LDL (mg/dL)	101.7 ± 29.19	94.79 ± 78.91	99.02 ± 27.99
Leptin (ng/mL)	2.49 ± 2.08	3.13 ± 1.96	1.63 ± 1.94
Visfatina (ng/dL)	1.23 ± 0.42	1.29 ± 0.34	1.11 ± 0.45
HDL: High Density cholesterol (for its acronym in English), LDL: low density cholesterol.			

The data show that men have the highest BMI, as well as triglycerides. On the other hand, leptin and total cholesterol values are higher in women than in men.

Subsequently, we proceeded to stratify the data according to leptin levels in hyperleptinemia and normal leptin. The results can be seen in Table 6.2.

Table 6.2 Biochemical parameters stratified according to leptin value

Parameter	Hyperleptinemia	Normal leptin	Value p
Age	20.48 ± 1.40	20.64 ± 1.71	0.8306
IMC	30.54 ± 6.80	24.73 ± 5.28	0.0000*
Glucose (mg/dL)	83.71 ± 7.64	85.30 ± 8.44	0.3362
Total Cholesterol (mg/dL)	177.74 ± 44.78	165.94 ±32.36	0.0900
Triglycerides (mg/dL)	105.17 ± 46.71	97.47 ± 53.45	0.4665
HDL (mg/dL)	46.94 ± 13.93	46.86 ± 12.30	0.9773
LDL (mg/dL)	110.43 ± 38.23	99.77 ± 26.55	0.0653
Leptin (ng/mL)	5.87 ± 2.22	1.74 ± 1.06	0.0000*
Visfatina (ng/mL)	1.27 ± 0.46	1.22 ± 0.42	0.6590
HDL: High Density cholesterol, LDL: low density cholesterol. *statistically significant			

We observed that the group with hyperleptinemia had higher BMI, cholesterol, triglycerides, LDL and visfatin values compared to the group with normal leptin values.

Finally, we proceeded to perform the association between leptin and visfatin with obesity and the results we found are reported in Table 6.3.

Table 6.3 Association of leptin and visfatin with obesity

Parameter	OR	Value p	IC
Leptin	5.866	0.001 *	2.552 – 13.50
Visfatina	0.2901	0.0201 *	0.0963 – 0.8737
OR: Odds Ratio, IC: Intervalo de Confianza. p < 0.05 Considerado como significativo			

It is observed that hyperleptinemia is a risk factor for the development of obesity with an OR of 5.86 (p=0.01), while visfatin acts as a protective factor with an OR of 0.2901 (p=0.02).

6.4 Discussion

The health significance of body fat has been constantly modified according to changes in the living conditions and expectations of each population group. As may be the role of abdominal obesity as a direct contributor to metabolic and cardiovascular risk is not yet systematically incorporated into the classical assessment of cardiometabolic risk. On the one hand, the cut-off points for waist circumference in different races are controversial. (Rosales, 2012)

Structural changes in adipose tissue lead to the release by adipocytes of cytokines called adipocytokines, as well as the mobilization and activation of leukocyte subpopulations, which can also release various mediators, helping to establish the inflammatory process and impair insulin sensitivity locally. In turn, these molecules manage to reach the systemic circulation, where they damage other organs such as the liver and skeletal muscle, causing damage to macronutrient metabolism, leading to the development of metabolic diseases such as metabolic syndrome, which in turn increases the possibility of triggering chronic degenerative diseases. (Vega-Robledo *et al*, 2019)

It is now fully demonstrated that adipose tissue, which includes adipocytes, macrophages, fibroblasts and other cell types, is a source of numerous molecules with different action profiles. Some adipokines such as leptin and adiponectin are preferentially produced by adipocytes, while others of an inflammatory nature, such as TNFα and IL-6 involved in inflammation and IR phenomena, are predominantly secreted by macrophages. (Vega-Robledo *et al*, 2019)

In our study we found an association between leptin and obesity with an OR of 5.86, establishing it as a risk factor for the development of this pathology. On the other hand, visfatin, in our study, was found to be a protective factor with an OR of 0.29..

The association with leptin has been reported in other studies and its role in the development of obesity is known; however, the mechanism by which it exerts its function is still under investigation. With respect to what was reported in our work, we can identify that elevated leptin levels have a negative role in health, since we found an increase in BMI, triglycerides and cholesterol.

In relation to the present study regarding the role of visfatin, there is great controversy due to the diversity of results that have been obtained, such as a study carried out in young adult patients with obesity, an association can be applied between the blood concentration of visfatin in patients without metabolic syndrome and with increased visceral adipose tissue, compared to those without metabolic syndrome and with normal visceral adipose tissue, a relationship that could not be observed in persons with the presence of metabolic syndrome. The authors concluded that the increase of resistin in patients with increased visceral adipose tissue without metabolic disease could indicate in some way that these individuals may present metabolic alterations in the future, since resistin has been shown to promote the production of inflammatory cytokines and has been pointed out as a marker of metabolic disease. (Rodríguez- López, 2015)

However, other researchers have not observed a relationship between metabolic markers and the levels of this adipocytokine, and it has even been found to be decreased in people with obesity. Al-Suhaimi *et al*, 2013; Cao H. *et al*, 2014; De Luis *et al*, 2010; Carvalho *et al*, 2014. Similarly, in other research with obese children, no correlation of visfatin levels with weight reduction, response to physical activity, body fat content or insulin resistance indices was found. (Martos-Moreno *et al*, 2013) On the other hand, in a similar study in obese children, serum resistin levels were related to central obesity and insulin resistance. (Sypniewska, 2015) This could be due to the stage of life being developed by the study participants, as well as gender.

With all that has been pointed out, it could be said that the excessive accumulation of body fat has a high impact on the health of obese individuals, negatively affecting their physical condition, vitality and, in general, their quality of life and thus their health. These alterations can be avoided to try to contain the obesity epidemic and prevent the increase of the negative consequences associated with obesity, since it has been predicted that if the trends of the increase of this condition continue as they have after the beginning of the century, the world will not meet the global objective to stop this epidemic. (Vázquez *et al*, 2013) Prevention must be effective to achieve restoration of homeostasis (cardiovascular and metabolic). (Collaboration NCDRF, 2016)

6.5 Conclusions

As a research group, we concluded that it is essential to have prospective studies that report on the predictive nature of the pathogenesis of obesity as soon as possible. In this case, therapeutic intervention in the early stages prior to the onset of metabolic complications could have a favorable cost-benefit ratio. Likewise, the incorporation of markers such as LDL particle size, insulin resistance index, proinflammatory adipocytokines such as leptin and visfatin may improve the current predictive capacity.

On the other hand, obesity not only leads to problems such as cardiometabolic diseases, but also influences the immune system in many ways. Obesity causes chronic low-grade activation of the immune system. When someone with this pre-existing condition is confronted with infectious processes, this could lead to a hyperactivation of the immune system, but in a detrimental way that does not fight the infection.

The situation currently being experienced with the COVID-19 pandemic has made us aware of the complex interactions of obesity with infectious diseases and the gaps in our understanding of how chronic health conditions affect our immune responses to acute infection. Finally, we are observing the rise of infections among young adults creates a "reservoir of disease" that eventually "spills over into the rest of society," one that has not yet achieved herd immunity, and portends a broader increase in cases. Fortunately, the chance of dying from COVID-19 remains very small for people under the age of 50, but this age group can become severely ill or suffer long-term symptoms after initial infection. People with underlying conditions, such as obesity and heart disease, are also more likely to become seriously ill.

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