Relationship between leptin and hypertension

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ABSTRACT

Leptin is secreted primarily by white adipose tissue and secondarily in-outrown fat. It participates as a satiety signal in the regulation of food intake. It promotes insulin resistance as well as nitric oxide –mediated vasodilation increasing the activity of the sympathetic system. Leptin stimulates insulin secretion out of adipose tissue too. This work was carried out to study how leptin affects the maintenance of hypertension and Diabetes mellitus type 2. Objective: to describe the interaction between leptin, diabetes and hypertension on healthy patients, the hypertensive diabetics type 2 as well as the relationship between leptin, non invasive hemodynamical variables and metabolic diseases. Methods: A crossed-comparative observational design research was done with 75 subjects who were selected and divided into three groups of 25 participants: Healthy, diabetics type 2 and hypertense. Patients were measured: anthropometric parameters, systolic blood pressure (SBP), diastolic blood pressure (DBP), and medial blood pressure (MBP). Biochemical variables as: insulin, glocose, HbA1c, HOMA-IR and leptin data were statistically analysed and described. Similarly, SBP, DBP and MAP were in the three groups (P>0.05). Conclusions: Leptin showed high levels in diabetic and hypertensive patients when compared with control group. The SBP, DBP.and MBP were altered in both diabetic and hypertense subjects resulting from the sympathetic system activation throughout leptin activity. In short, Diabetes type 2, which is an insulin resistance state, may be influenced by leptin levels as well as its relation with Diabetes Mellitus type 2 (DM2), and High blood pressure, (HBP).

Key Words: Leptin, Diabetes M type 2, Hypertension and Insulin Resistance.

INTRODUCTION

Over last decades it has been concluded that adipose tissues are not only energy deposits but a source of metabolic active substances as well: alfa tumoral necrosis (FNTa), angiotensinogen, prostateglands, strogens, and the product of the gen, that is, leptin1. Leptin is a peptide-hormone of about 167 aminoacids transcribed by the gen ob. Its name comes from the greek word LEPTOS, which means; "thin" [2].

This hormone is primarily secreted by the white adipose tissues; smaller quantities of fat are also found withn brown fat. It Works out Characteristically as a satiety signal, which acts over the hipotalamus, so that it goes throughout the hematoencefalic fense and also intervenes upon the signals that regulate food intake. It mainly inhibits the synthesis of an affectanting molecule. NPY (neuropeptide Y), which is a powerful stimulus response to apetite.

A circadian rithm is presented by leptin liberation with plasmatic concentrations sligghtly higher during day in man and at nights in rats.Leptin in adiposites regulated at a transcriptional level, depending on the amount of adipose white tisue and adipose size. Moreover, its expression and the the seric level increase after intake and is cut out rapidly with fasting, which if longer, the amount and size of the adipose tissue, is considerably reduced. Although body fat is the main factor of seric leptin levels, its secretion is regulated by several elements. Insulin is the best highlighted among them. It enhaces its generation out of the adipose tissue as live as well as in vittro[3-5].

Leptin gets most of its metabolic effects by interacting with specific receptors located within the central nervous system and peripherical tissues. These otherwise, are expressed in other tissues such as kidneys, cardiovascular system, hepatocytes, hematopoyetic cells and pancreatic islets. It is in this particular reason (peripherical receptors existence) within which leptin has come to play a principal roll, according to its relationship between obesity and high blood pressure HBP; It is also a controller and a metabolic unifier[6].

Relationship between obesity and Hypertension is highly documented since several years ago[7-10]. Given this strong association, it has been said that adipose mass, serves as an important tissue over blood pressure regulation (BP); Eventhogh the underlying mechanism of this theory is not fully confirmed yet, however, leptin has been pointed out as the bridge linking these two entities[11].

On the other hand, when sympatic terminations are removed from blood vessels and in so doing leptin is administrated, a vasodilation is produced, which has been related to the increase of nitric oxide synthesis in a depending doses form; this Nitric Oxide (NO) synthesis strenghened by leptin, takes part within the endothel, reason why it is also known as NODE, that is, Nitric Oxide derived from the Endothel. So, the endothel is considered as a Paracrine organ, for it generates and liberates a huge quantity of elements with relaxing and contráctil effects. Anyway, discussion has been focused not only on nitric oxide (NO), as being the unique responsible component which causes vasodilation, but as a cascade of events that finally lead to an endothelial malfunction, in which other elements are likely participating, such as hyperpolarizing factor Endothellike Derived, (HPFED) [12-16].

Similarly, the chronical continuous administration of leptin in both modellike animals and humans with an untouched nervous system, generates a sustained increase over the sympatic system activity[12]. On leptin administered healhy volunteers, on effecting the vasodilation action product of Nitric Oxide (NO) secretion and the sympatic stimulation, an evident important change on blood pressure[16], is not observable. The increasing activity of this system has been quantified in various organs which include kidneys, brown adipose tissues and adrenalin glands.

The physiological meaning of this fact, is linked to metabolic and inmunological functions; the relationship with blood pressure relation is remarkable, for increasing the sympathetic activity a relaxing increase on blood pressure is enhanced[17-20].

In short, on this account, the balance between leptin pressure effects by means of sympatic activation and hipotensor vasodilation effect, will determine leptin influence upon regulating blood pressure. Furthermore, apart from the above mentioned factors, leptin increases renal natriuresis; a mechanism which contributes to hypotension.

Consequently, interactions between leptin (L) and insulin, have been evaluated. For one side co-existence of resistance states to insulin and leptin in obese guys, and on the other hand a strong relationship between obesity and Diabetes Mellitus type 2 (DM2)[21-25]. It´s already known that DM2 is highlighted for its resistance state to insulin, associated hiperglucemia which at the same time permitted to postulate that leptin is one of the factors ralated to obesity and insulin resistance, and between obesity and DM2. It has been demonstrated that in rats adipocytes, leptin diminishes insulin bonds with its receptors. Leptin and insulin control themselves ane another. Thus, leptin inhibits insulin production on B pancreas cells[25]. While in an other hand, insulin encourages leptin generation in adipose tissues.

Given that relationship between leptin, diabetes and hypertension is more evident each day, the following questions are appropriately posed: How Can Leptin Influence on Maintaining Blood Hypertension and Diabetes Mellitus type 2 ? What are leptin effects on non invasive hemodynamical variables of healhy subjects, diabetics type 2 and hypertense ones? These questions gave birth to the objectives ahead: 1) To describe interaction between leptin and diabetes, and also hypertension on healhy subjects, diabettics type 2 and hypertense patients.

METHODS

In order to accomplish the given objectives, a transversal and correlational analytical observational research was carefully designed. Elements to be studied were chosen from the universe coming from diabetes consultation at the Internal Medicine Department of the HospitalVictorino Santaella, located in Los Teques Estate Miranda on february 2008 and december 2009. Samples for the present research focused on a non intentional probabilistic type, by clinical criteria selection means; that is, including and excluding criterias. A definite sample was taken out of 93 patients as awhole, which was intentionally calculated in order to detect significative variation among the groups obect of study. It was assumed that it would not exceed 10% and in the meantime an important level of estimation of 5%. So a superior study of 80% was assumed. As a result, it implied the need of including 75 patients within the group of study. Inclusion Criterias: A five years data of diabetics types 2 since the diagnoses, also, a five years data of high blood pressure; and of course, the patient´s agreement to be included among the group of study ranging from 30 to 60 years of age.

Diabetes condition was defined by the American Diabetes Association, updated criterial terms, 2004. ("diagnoses and classification of Diabetes mellitus", 1997)[26], for diabetes mellitus classification, and so did, hypertension condition was, supporting on the VII National Committe Report recommendations hypertension disease, written by Chobanian et al in 2003[27]. This way, 75 subjects ranging from 30 to 60 years of age, either male of female, were selected in non probabilistic intention. The groups were distributed according to their clinical situation in three branches of 25

each: Helthy, diabetics type 2 and hypertense.

Once the clinical criteria sample was determined and the consent permission was granted, the second phase of study took place. The subjects of study showed up at the laboratory under requiered conditions, as follow: a) 14 full hours of fasting, b) two full days of resting with no body exercise. c) a five days of hypertense medical treatment suspensión, d) avoiding oral hypoglycemic intake, only on the day of study. Notice: if the patient prsented any sudden risky situation, the study would not take place, thus, postponed. Subjects were carefully studied following the present protocol:

A) Antropometric variables:

1. Weight measuring with a scale, 200kgs máximum capacity. Subject should be weighed naked and without shoes at all (if possible). The results were shown in kilograms.

2. Measued with a high stick expressed in centimeters and inches, height ranging betwen 75 to 200 cmts, heel foot measurement with an altimeter in naked foot, upright streched, straight head with the back facing the altimeter and feet and knees paired, ankles in a flat position.

3. Body mass index (BMI): weight and height are related to the conditioning of World Health Organization (WHO)[28] criterias for obesity were the tools for establishing the criteria of obesity.

4. Heap and belly measurement besides abdominal belly relation: measurement was realized three times. So patterns or referents were considered as follows: Belly circumference ≥ of 90 Cmts for man and ≥ 80 Cmts for woman in Latin America[29].

B) Non Invasive Cardiovascular Variables

1. Systolic blood pressure (SBP), Diastolic blood pressure (DBP), and medial blood pressure (MBP) was observed by esfignomanometer of mercury with small handle dynamap of 48X14 cmt; the patient without prior coffee intake nor cigarette consumption, and previous one hour blood pressure measurement, in agreement to the techniques already described[30,31].

C) Biochemycal Variables: the biochemycal analysis already studied, product of samples taken at 0′, 30'

1. Insulin by RIA methods, Radio Inmmune Assay. (Owen and Roberts, 2004) [32].

2. Glucemy: coloredmetric enzimatic method, comercial kit from CIENVAR, (Bergmeyer, 1972)[33].

3. Glicosilated Hemoglobin HbA1c: resin method of coloredmetric enzimatic ionic, interchange, Bioscience commercial laboratory kit. (Sacks et al., 2002; Trivelli et al, 1971) [34,35].

4. HOMA-IR: mathematic model-like calculated (Matthewa et al, 1985, Turner et al, 1990) [36,37].

5.- Leptin: by RIA Method, Radio inmune Assay kit provided with by Diagnostic system Laboratories", 445 Medical Center Blvd, Webster Texas 77598-4217 USA. Catalog number: DSL23100 (Blum et al, 1997 and Malmstrom et al, 1996) [38,39].

Experimental design: the day of study the patients' periferial single veins were cateterized with jelco N° 21, thus, samples were taken at 0', and the solution 0,9% administration took place; consequently, at the last 30 minute, blood samples were taken off again.

Techniques and tools for data recollection

A structured or formal observation and a survey as a selection technique for patients were used. It was technically assisted in a pre-selected laboratory. Pre-selection of subjects to be investigated was done by means of a self elaborated questionnaire over cardiovascular risky factors and the diabetes consult (FRCED) at the Internal Medicine Department of Victorino Santaella Hospital previous written consentment of patients.

Researchers realized the observation of subjects who participated in the study by using an observation guideline of non invasive hemodynamic and anthropometrical variables and (VNI-A) in order to to get measurement data of blood pressure, pulse, heart frequency, weight, size, belly size, and heep, They were technically assisted with measurement tools previously reordained.

Statistical Analysis

The study of both biochemical and hemodynamical variables was realized throughout descriptive statistic, that is, (media, standard deviation, frequencies and percentages. In order to prove if variables would either follow or not a normal distribution a parametrical test Kolmogorov-Smirnoff to measure normality was applied. On the other hand, in the case of variables which responded to a normal distribution, the "t"student test was applied for paired samples and for those ones which did not repond to a normal distribution, the parametric test of Wilcoxon was applied. The afterward contrasts among groups, were based on Bonferroni's test; similarly, differencies among researching aspects were lineal contrast based. Correlative points among varied factors were based on non parametric co-relation co-effecients serial typelike. At last, It was considered as a significant statistical value: if $p < 0,05$ and highly significant if $p < 0,01$.

RESULTS

Table N°. 1 Highlight samples according to studied groups.

	Groups				
Variables	Healthy(1)	Diabetics(2)	Hypertense(3)	P	Variation among Groups
N	25	25	25	-	-
Age (*)	35,6 ± 7,2	44,0 ± 8,4	42,8 ± 7,1	< 0,05	1-2; 2-3
HOMA (*)	1,74 ± 0,95	5,63 ± 3,76	2,41 ± 1,21	< 0,05	1-2; 2-3
HbA-1c (*)	6,31 ± 0,64	7,86 ± 1,62	6,01 ± 0,9	< 0,05	1-2; 2-3
BMI (*)	25,3 ± 3,0	29,6 ± 5,5	28,7 ± 6,1	< 0,05	1-2
HBI (*)	1,00 ± 0,13	0,95 ± 0,06	0,95 ± 0,08	ns	-
Sex				ns	
Male	8 (32,0%)	15 (60,0%)	13 (52,0%)		
Female	17 (68,0%)	10 (40,0%)	12 (48,0%)		

(*) Media expressed values ± Standard deviation.

Table N° 2 Hemodynamical Variables: SBP, DBP, and MBP. Variation of Values among Groups.

	TRACKING					
GROUPS	SBP 0' 30		DBP ' 0' 30'		MBP 0' 30	P
HEALTHY	117 ± 10	118 ±11	72 ± 9	73±8 90±8	88±18	0,05
DIABETICS	130 ± 14	130 ± 14	81 ± 9	80±9 99±11	98±9	0,05
HYPERTENSE	145 ± 14	150 ±18	89 ± 10	92±9 107±9	110±8	0,05

(*) Media expressed values ± Standard deviation.

Table N° 3 Glycemic Concentration Variation According to Groups.

Groups	0'	30'	P	Intragroup Differences
Healhy(1)	86 ± 9	98 ± 21	< 0,05	all of them
Diabetics (2)	121 ± 42	118 ± 35	< 0,05	all of them
Hypertense (3)	91 ± 11	103 ± 20	< 0,05	all of them

(*) Media expressed values ± Standard deviation.

Table N° 4. Leptin Value Differencies According to groups

	Tracking			
GROUPS	0'	30'	P	Intragroup differencies
Healhy(1)	8,4 ± 3,0	8,7 ± 3,3	Ns	-
Diabetics(2)	13,0 ± 4,5	11,7 ± 4,2	< 0,05	1-2; 1-3; 2-3
Hypertense(3)	14,3 ± 8,6	13,5 ± 7,7	Ns	-

(*) Media expressed values ± Standard deviation.

(*) Media expressed values ± Standard deviation.

Table N°. 5 Leptin Value Differences According to Sex and Groups Studied

Grupos	Sexo		Leptina basal	Leptina 30 minutos
Sanos	Masculino	N	8	8
		Media	6,924	6,849
		Desv. típ.	3,6816	4,1285
	Femenino	N	17	17
		Media	9,130	9,622
		Desv. típ.	2,4311	2,5969
	Total	N	25	25
		Media	8,424	8,734
		Desv. típ.	2,9995	3,3482
Diabeticos	Masculino	N	15	15
		Media	11,322	10,039
		Desv. típ.	3,7970	3,2491
	Femenino	N	10	10
		Media	15,523	14,287
		Desv. típ.	4,4341	4,2996
	Total	N	25	25
		Media	13,002	11,738
		Desv. típ.	4,4939	4,1954
Hipertensos	Masculino	N	13	13
		Media	13,770	12,934
		Desv. típ.	7,2102	7,2851
	Femenino	N	12	12
		Media	14,793	14,148
		Desv. típ.	10,2086	8,4281
	Total	N	25	25
		Media	14,261	13,517
		Desv. típ.	8,6042	7,7121

DISCUSSION

This is in order to determine the characteristics according to age, sex, HOMA, HbA1c and anthrometric group of healhy patients. Diabetic and hypertense on basal conditions. On table 1, 75 patients between 35 and 44 years of age were studied. Also, 39 female subjects and 36 male ones were evaluated. The body mass index(BMI)of the population studied, fluctuated between 25,48 and 27,84 kg/m2. Glicosilated hemoglobin A1c ranged between 6,42 and 8,49% in the main group. In the same way, the hip, belly index varied 1,00 to 0,95 on the population studied. Significative differences in regard to age, HOMA, HbA1c and MMI were obtained.

The systolic blood pressure (SBP), diastolic blood pressure (DBP) and media blood pressure (MBP). (Table 2) show up p < 0,05 values when contrasted healhy guys to diabetic ones; Healthy against hypertense, and diabetics against hypertense. It also revealed significative differences (p < 0,05) over leptin values at 0 minute. When contrasting healthy groups with diabetic and hypertense, (table 4). Leptin hypotalamic effects would consequently get an increase over blood pressure by the sympatic nervous system activation[40], while the vascular direct effect that exercises over the receptors present on the muscular tissue[41] and over the vascular endothel, it would result in a vasodilation effect. Leptin induces a direct vasodilation throughout endothelial mechanisms which differ in function of varied vascular facts. In conducting vessels as rat´s aorta, leptin induces vasodilation or widening vessel by liberation of NO throughout endothelial NOS activation by means of fosforilación of protein serina/treonina quinasa[42]. On the contrary on resistant vessels like mesenteric arteries, leptin vasodilation effect is produced by EDHF liberation on account of that relaxation mediated by leptin lessens in presence of the EDHF inhibitor. On the other hand, Rodriguez and Cols (2007)[43], have recently suggested that leptin produces vasodilation by means of direct effect over medial tissues when blocking calcium entrance to vascular soft mussel cells induced by Ang II, and diminishes the contractible respond on account of Ang II, when increasing the production of NO over vascular soft mussel cells by means of induceable NOS. It is also known that, both leptin and insulin work together in the vascular modulation tone. Insuline empower induced vasodilation by leptin, increasing liberation of NO; at the same time growing up phosphorylation of endothelial NO. On the other hand, leptin is implied in the aterogenic process of favoring both plaque agregation and trombosis; inflammatory citokins production like TNF-α, IL-6, and IL-12; promote the NEOINTIMA increase; entice the production of anions of mitocondrias superoxide in endotelial aorta cells, and vascular soft mussel cells calcification[44].

Significative variation was observed (p<0,05) for glycemic, upon healhy groups, diabetic and hypertense at 0´, 30´ minutes of the study and when comparing healhy groups with diabetic ones, healhy versus hypertense and diabetics versus hypertense at 0´, and only on healhy groups versus diabetic ones at the 30th minute of the study. Similarly, significative differences (p<0,05) for insulin on healhy groups, diabetic and hypertense at 0´, 30´ minutes of the study and when contrasting healhy groups versus diabetics and diabetics versus hypertense upon minute 0´. Both glycemic and insuline on the three groups of study give date that support a close malfunctioning relationship with between both glycemic and insulin. Such discovery confirmed when contrasting HOMA value upon healhy versus diabetics and these versus hypertense. As it is already commented, DM2 hightlights itself for an insulin resistant state parallel with hiperglucemia.

Greenfield[45], has evaluated the interaction between leptin and insulin, either for insulin resistant states of co-existence and to leptin in obese guys, or the strong association between obesity and diabetes mellitus type 2(DM2), which has led Greenfield JR to postulate et al, that leptin is one of the factors of relatioship between obesity and insulin resistance and between obesity and DM2. It has been proven that on rat´s adipocytes, leptin lessens the insulin bond with its receptors[46], thus fomenting insulin resistance. Both leptin and insulin regulate themselves one another. Thus, leptin inhibits insulin production on pancreas B cells, while insulin entices leptin production on the adipose tissue[47,48]. So it is worth posing that hyperleptinemia might be a crucial factor upon insulin resistace regarding most on obese patients. Due to insulin plasmatic levels which are highly related with the amount of adipose tissue, when mussel mass index of the people studied was evaluated, this fluctuated between 25,48 and 27,84 kg/m^2, that is, the population object of study, was not obese; it might likely influence on leptin values registered.

On table 5, we observe the comparison between studied group sex and leptin values in each group of patients. The diabetic ones show p=0,014 at minute 30. The hypertense groups did not show relevant results.

Pearson´s co-relation and leptin according to age, HOMA resulted with no important interest or whatsoever in the study. Pearson´s co-relation of systolic blood pressure (SBP) and leptin was: -0,517 and p: 0,008 at minute 30 upon the diabetic group of patients. Similarly, Pearson´s co-relation with diastolic blood pressure (DBP) and leptin was: -0,469 and p: 0.018 at minute 30 on diabetic group of patients. Contrary to researchers´findings, results reported by Velázquez-Maldonado and Col, 2006[49], whom in the study: Relationship between leptin and blood pressure on non diabetic guys Likely effect of age and sex, proved that systolic blood pressure was sigficantly higher upon under 50 age males; it was rather higher over 50ths on women; DBP showed a similar pattern, but on older than 50, important differences between both sex were not observed. Both SBP and DBP were related to body mass index and hip belly relation on both sexs and outstanding only with female sex. Relationship between leptin and blood pressure, either systolic or diastolic was significantly only on

men. With the analysis of multiple regression it was confirmed that age in women and leptin in men are the unique variables that regulate blood pressure. Researchers concluded that in non diabetic subjects, blood pressure is related with leptin in man and age in woman.

CONCLUSIONS

1. Resent obtained discoveries give evidence of significant higher values of leptin on diabetic and hypertense patients when contrasted with healhy ones. Leptin is implied within the aterogenic process on encouraging plaquetary agregation and trombosis, inflammatory cytokine production, like: TNF-α, IL-6, and IL-12. Adipose tissue segregates a variety of factors which contribute to insulin resistance and endothelial malfunction.

2. Non invasive variables (SBP, DBP, MBP) are found altered in diabetic and hypertense patients. The increase of blood pressure corresponds to the sympathetic nervous system activation. Nevertheless, co-relations between leptin and hemodynamical variables were signicantly inverse, just on the group of diabetic patients type 2.

3. It is evident that there is a relationship in diabetics type 2 highlighted by an insulin resistance state associated to hyperglycemia, hence permiting the postulation of: leptin or so called hyperleptiness, which is one of the factors on relationship between insulin resistance, SBP and Diabeted Mellitus type 2 (DM2).

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