Relation of serum leptin level to hypertensive retinopathy

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Abstract

Leptin plays a promoting role in angiogenesis and the vascular endothelium express the long form of leptin receptor, therefore, the aim of the work was to assess the plasma level of leptin in hypertensive patients and to evaluate the relationship between its concentration and hypertension. and hypertensive retinopathy, also to assess its relation to body mass index. This study was carried out on 50 patients with essential hypertension and 25 normal healthy, age and sex matched control subjects. Patients with essential hypertension were classified into 2 groups according to the presence or absence of retinopathy, 25 patients without hypertensive retinopathy (Group II a) and 25 patients with hypertensive retinopathy (Group II b).

The study showed significantly very higher serum leptin in group II and its subgroups ( II a and II b) compared to those of the control (Group I), despite no significant difference was detected between the three groups (group I ,II a and II b) regarding age, sex and body mass index. Also no significant deference was detected between hypertensive group without retinopathy and hypertensive retinopathy group as regard mean blood pressure.

Positive correlation between serum leptin level and mean blood pressure among all groups was found. Also positive correlation between serum leptin level and body mass index (BMI) among all groups.

Introduction

The pathophysiological mechanism of hypertensive retinopathy is not fully established. The autoregulation of retinal circulation failed as the blood pressure increased beyond the critical limit. Also humoral components may be involved as well (Lowenthel and Zimlichmun, 1993).

Leptin is a hormone (167 amino acid protein) secreted primarily by adipocytes mainly in adipose tissue, gastric epithelium and placenta. It plays an important role in regulation of blood intake and energy expenditure (Korbonits et al 2001). It increases the vascular permeability through stimulation of short form receptors (Cao et al 2001). Leptin induces endothelial cells migration which is the key event in angiogenesis (Goetze et al 2002). Yamagishi et al (2004). attributed the development and progression of retinopathy to loss and dysfunction of pericytes.

Aim of the study:

Is to evaluate the plasma leptin level in relation to the grades of hypertensive retinopathy and also to assess its level in hypertensive patients and its relation to their body mass index.

Subjects and methods

This study was done on 50 patients with essential hypertension (24 males and 26 females) with mean age of $45.54 \pm 4.32$ years compared to 25 healthy normotensive subjects age, sex and body mass index matched as control group (12 males and 13 females), with mean age of $44.20\pm3.86$ years.

The included subjects were classified into two groups:

Group I: 25 healthy normotensive subjects as control
**Group II:** 50 patients with essential hypertension, they were divided according to the presence or absence of retinopathy into two subgroups:

**Group II a:** 25 patients without hypertensive retinopathy
**Group II b:** 25 patients with hypertensive retinopathy.

Patients with diabetes mellitus, ischemic heart diseases heart failure, chronic renal or liver diseases and psychological disturbances were excluded from this study as these may affect plasma leptin level.

Full history and complete clinical examination were done for all patients and control with stress on age, sex, systolic, diastolic and mean blood pressure (MBP) which equals diastolic blood pressure +1/3 pulse pressure) and body mass index (weight in Kg /height 2 in meter),heart, chest and abdominal examination.

Ophthalmological examinations were done and included:-

- visual acuity measurement
- Intraocular pressure measurements
- Fundus examination and fundus photography (coloured) and fundus fluorescein angiography.
- We use grading stated by Kanski (1999) of patients with hypertensive retinopathy as follow:

**Grade I:** consists of mild generalized arteriolar attenuation, particularly of small branches, with broadening of the arteriolar light reflex and vein concealment.

**Grade II:** More severe generalized as well as focal arteriolar narrowing with deflection of veins at arteriovenous (A/V) crossings Fig (2).

**Grade III:** Copper wiring of arterioles, banking of veins distal to A/V crossing and right angled deflection of veins flame shaped haemorrhages and exudates either hard or cotton-wool

**Grad 4:** Changes as grade 3 in addition to disc swelling and silver-wiring of arterioles

**NB:** Only patients with grades 1 and 2 hypertensive retinopathy were included, as patients with advanced stages of retinopathy were not included because most had renal and cardiac complications that could influence the plasma leptin level.

**Laboratory investigations:**
- Fasting and 2 hours blood glucose levels
- Kidney function tests
- Liver functions
- Lipids profile
- ECG to exclude any heart problems.
- Determination of serum leptin in ng/ml was done using diagnostic bio Canad Inc (dbc) No: 4260 cat by enzyme linked immunosorbent assay bits (ELIZA).
- NB: Statistical analysis was done by using mean, standard deviation (SD), minimum and maximum values and P value.

**Results**

This study was conducted on 50 patients with essential hypertension (group II) and 25 healthy normotensive age, sex and BMI matched subjects as control group (group I).

The main clinical symptoms was headache in 25 patients (50%), 3 patients (6%) had epistaxis while 12 patients (24%) had no symptoms and known to have hypertension while 10 patients (20%) accidentally discovered to be hypertensive.

The age of patients (Group II) ranged from 38 to 55 years with a mean SD of 45.54±4.32 years. Twenty four (48%) were male and 26 (52%) were female. The mean ± SD of their body mass index (BMI) was 26.26±4.41.

The hypertensive patients were divided into two groups according to the presence (IIb) or absence (IIa) of hypertensive retinopathy.

The mean ± SD of mean blood pressure (MBP) were very highly significantly increased in hypertensive group (II) (126.13 7.81) than that of control group (I) (88.19 6.28) (P < 0.001) and no significant difference in mean ± SD of MBP of group IIa versus group IIb were found (table 1).

The mean ±SD of serum leptin level were very highly significantly increased in hypertensive group (II) (29.74±22.46 ng/dl)
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compared to the control group (I) (7.06±4.87 ng/dl) and in group IIb versus group I while highly significantly increased in group IIa (22.62±19.85) versus group I (7.06±4.87) (p<0.01) and significant increase in group IIb (36.86±23.03) versus group IIa (table 2).

As regard BMI, there was no significance difference of mean ± SD of BMI of group IIa and IIb versus control and group IIa versus group IIb. There was positive correlation between serum leptin level and also BMI (table 3) and MBP (table 4) in all groups I, IIa, IIb.

Table (1): Mean values of MBP among all studied groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD of MBP</th>
<th>p. value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>88.19 ± 6.28</td>
<td>&lt; 0.001</td>
<td>V. H. S.</td>
</tr>
<tr>
<td>II</td>
<td>126.13 ± 7.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>88.19±6.28</td>
<td>&lt; 0.001</td>
<td>V. H. S.</td>
</tr>
<tr>
<td>IIa</td>
<td>125.15±7.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>88.19±6.28</td>
<td>&lt;0.001</td>
<td>V. H. S.</td>
</tr>
<tr>
<td>IIb</td>
<td>127.11±8.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>125.15±7.15</td>
<td>&gt;0.05</td>
<td>N. S.</td>
</tr>
<tr>
<td>IIb</td>
<td>127.11±8.47</td>
<td></td>
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</tbody>
</table>

Table (2) Serum leptin among all studied groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD of serum leptin</th>
<th>p. value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7.06 ± 4.87</td>
<td>&lt; 0.001</td>
<td>V. H. S.</td>
</tr>
<tr>
<td>II</td>
<td>29.74 ± 22.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7.06 ± 4.87</td>
<td>&lt; 0.01</td>
<td>H. S.</td>
</tr>
<tr>
<td>IIa</td>
<td>22.62 ± 19.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7.06 ± 4.87</td>
<td>&lt;0.001</td>
<td>V. H. S.</td>
</tr>
<tr>
<td>IIb</td>
<td>36.86±23.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>2.62 ± 19.85</td>
<td>&lt;0.05</td>
<td>S.</td>
</tr>
<tr>
<td>IIb</td>
<td>36.86±23.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table (3) Correlation between serum leptin level and body mass index (BMI) among all groups

<table>
<thead>
<tr>
<th>BMI</th>
<th>R. value</th>
<th>P. value</th>
<th>significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group II</td>
<td>0.445</td>
<td>&lt; 0.05</td>
<td>S</td>
</tr>
<tr>
<td>Group I control</td>
<td>0.481</td>
<td>&lt; 0.05</td>
<td>S</td>
</tr>
<tr>
<td>Group IIa</td>
<td>5.437</td>
<td>&lt; 0.05</td>
<td>S</td>
</tr>
<tr>
<td>Group IIb</td>
<td>0.470</td>
<td>&lt; 0.05</td>
<td>S</td>
</tr>
</tbody>
</table>
Table (4) Correlation between serum leptin level and mean blood pressure (MBP) among all groups.

<table>
<thead>
<tr>
<th>MBP</th>
<th>R. value</th>
<th>P. value</th>
<th>significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group II</td>
<td>0.492</td>
<td>&lt; 0.01</td>
<td>H.S</td>
</tr>
<tr>
<td>Group I control</td>
<td>0.410</td>
<td>&lt; 0.05</td>
<td>S</td>
</tr>
<tr>
<td>Group IIa</td>
<td>0.485</td>
<td>&lt; 0.05</td>
<td>S</td>
</tr>
<tr>
<td>Group II b</td>
<td>0.477</td>
<td>&lt; 0.05</td>
<td>S</td>
</tr>
</tbody>
</table>

P > 0.05 N.S. "No significant"
P < 0.05 S. "Significant"
P < 0.01 H.S "Highly significant"
P < 0.001 V.H.S "Very highly significant"

**Discussion**

Epidemiological studies have clearly demonstrated that elevated blood pressure is a major cause of premature vascular disease leading to cerebro vascular events, ischaemic heart disease and peripheral vascular disease (Kumar & Clark 2002).

Hypertensive blood vessel damage in the eye is linked with similar changes in brain and has been shown to be associated with higher risk of stroke and death (Kumar and Clark, 2002).

The pathogenesis of essential hypertension remain unclear but increase in body weight most of time is associated with hypertension also there are several reports indicating that leptin may have a role in...
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hypertension (Canatan et al., 2004).

Leptin plays an important role in regulation of food intake, energy expenditure and body weight regulation (Havel, 2000). It was expressed in adipose tissue, gastric epithelium, skeletal muscle (Ahima and Flier, 2000) and brain (Korbonits et al., 2001). Plasma leptin level correlated with body fat content. It is elevated in obesity and decreased in anorexia nervosa. Moreover it has been shown that in addition to its effect on food intake and energy expenditure, leptin affects autonomic, cardiovascular, renal and endocrinial functions (Korbonits et al., 2001).

It has also recently been shown that leptin plays a promoting role in angiogenesis and that vascular endothelium expresses the long form of leptin so leptin might contributes to end organ damage in hypertension (Uckaya et al, 2000). In the present study we evaluated the relationship between plasma leptin concentration and hypertensive retinopathy.

Fifty patients with essential hypertension and 25 healthy normotensive control subjects matched for age, sex and body mass index were enrolled in the study. For assessment of retinopathy according to Kanski (1999) grading direct and indirect ophthalmoscope and fundus fluroescein angiography (FFA) were performed on hypertensive group. Twenty five patients had hypertensive retinopathy and 25 patients had normal fundus. Our work demonstrated significantly very higher serum leptin in patients with hypertension (Leptin 29.74±22.46) compared to those of control group (7.06±4.87), (P value <0.001) despite no significant difference was detected between the twogroups regarding body mass index and mean blood pressure (p< 05). Our results are in accordance with Hirose et al., (1998) who reported positive correlation between leptin and mean blood pressure also after adjustment for age and body mass index. Stefan et al., (1998) and Suter et al., (1998) showed that subjects with stage I hypertension had significantly higher plasma leptin level than normotensive subject. also showed that serum leptin concentration correlated with systolic and diastolic blood pressure. While Kennedy et al., (1998) demonstrated a relationship between elevated systolic blood pressure and diastolic blood pressure and plasma leptin level in hypertensive men only. Markis et al., (1998) demonstrated higher leptin and insulin level in healthy offspring of patients with hypertension compared to healthy offspring of normotensive patients which may reflect genetic bases of hypertension. Barba et al., (2003) and Eikelis et al., (2004) reported that plasma leptin level correlated with mean blood pressure independent of body mass and body fat content These results is supported by the action of leptin as it increases sympathetic activity (Anisley et al., 2003) and increases plasma renin, aldosterone, angiotensinogen release (Suter et al., 1998) also leptin induces the release of IL-6 from adipose tissues which in turn increases the C reactive protein from liver leading to endothelial dysfunction and decrease nitric oxide release (Undurti, 2002). The natriuretic effect of leptin is blunted in obesity and hypertension by increase renal sympathetic activity and by up regulating Na-K ATPases causing sodium reabsorption (Betowski et al., 2004).

In contrast neither Lonnqvist et al., (1997) Nor Mohammed Ali et al., (1997) found correlation between blood pressure and plasma leptin level. Narkiewicz et al., (1999) found that plasma leptin is significantly correlated with heart rate and diastolic blood pressure but not with 24 hours ambulatory systolic blood pressure in 60 men with essential hypertension. While Kokot et al., 1999 found no difference in plasma leptin level between hypertensive patients and control in a small sample of hypertensive patients. Rutkowski et al., (1999) found that ob gene is not a major contributor to phenotype of essential hypertension in African American.

The reason for divergent finding of these results are not obvious but may be due to factors such as race, selection criteria, limited numbers of patients, statistical methods, insulin resistance and difference antihypertensive treatment (Steinvinkel, 2000).

Also our work demonstrated significantly higher serum leptin level in patients
with hypertensive retinopathy compared to those of hypertensive patients without retinopathy ($P < 0.05$) and significantly very higher serum leptin in patients with hypertensive retinopathy compared to those of control group ($P < 0.001$), despite no significant difference was detected between three groups regarding body mass index ($P < 0.05$). Also no significant difference was detected between hypertensive group and hypertensive retinopathy group as regard mean blood pressure ($p < 0.05$). This data agree with a study performed by Uckaya et al., (2000) who stated that leptin was higher in patients with hypertensive retinopathy than patients with hypertension and control after correction for body mass index. The role of leptin in hypertensive retinopathy is supported by Bouloumie et al., (1998) who reported that leptin promotes angiogenesis in human umbilical venous cell and aortic endothelial cells. Sierra Honigmann et al., (1998) showed that leptin stimulates in vivo angiogenesis in the cornea also Yamagishi et al., (2004) reported that leptin stimulates vascular endothelial growth factor induction as well as pigment epithelium derived factor suppression both lead to parricides loss and dysfunction which is an early phase of retinopathy. Tanaka et al., (1999) reported that leptin induced endothelial cell migration which is a key event in angiogenesis also Cao et al., (2001) reported that leptin increases the vascular permeability. Konstantinides et al., (2001) reported that leptinpotentiates aggregation ofplatelet and formation ofthrombi.

Singhal et al., (2002) reported that High leptin level is predictive of poor vascular compliance which accompanied the atherosclerosis.

Our result demonstrated that there is significantly positive colt elation between serum leptin level and body mass index within the control group and Hypertensive groups, the same results was obtained by Leyva et al (1998); Yoshinari et al (1998) and Ruhi and Everhart (2001).

**Conclusion**

The same work may be done to study the possible improvement of retinopathy with restrict control of hypertension and obesity.

Researches must be continued for leptin antagonist to stop the end organ damage secondary to hyperleptinaemia in obese individual.

**Reference**


25. Rutkowski MP, Klanke CA, Su YR, Reif M et al.,(1999): Genetic markers at the leptin (OB) locus are not significantly linked hypertension in African Americans. Hypertension; 31: 12301236


علاقة مستوي اللبتن بالبلازما واختلال الشبكية الناتج عن فرط ضغط الدم الشرياني

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يعتبر اللبتن نتاج جين السمنة ويفترز أساسا من الخلايا الدهنية ونسبته في الدم
تعكس الطاقة المختزنة في الأنسجة الدهنية ويرتبط بعلاجت متبادل مع نماث كتلة
الجسم. ولللبتن العديد من الوظائف الحيوية التي قد تؤدي إلى ارتفاع ضغط الدم.
والهدف من هذا البحث قياس نسبة اللبتن بالبلازما في مرضى فرط ضغط الدم
الشرياني وعلاقةه بكتلة الجسم وقيمة العلاج بين نسبة اللبتن بالبلازما واختلال الشبكية
الناتج عن فرط ضغط الدم الشرياني وعلاقته أيضاً بمستوى ارتفاع ضغط الدم وهذه
الدراسة اجريت على 50 مريض يعانون من فرط ضغط الدم و25 شخص سليم
متوافقين في السن والجسم وكتلة الجسم كمجموعة ضابطة
وتم تقسيمهم كالاتي

المجموعة الأولى تشتمل 25 شخص سليم كمجموعة ضابطة
المجموعة الثانية تشتمل 50 مريض يعانون من فرط ضغط الدم الشرياني وقد تم
تقسيمهم الى مجموعتين جزئيتين
المجموعة الجزئية الأولى تشتمل 25 مريض يعانون من فرط ضغط الدم الشرياني
بدون اختلال شبكية العين الناتج عن فرط ضغط الدم الشرياني
المجموعة الجزئية الثانية تشتمل 25 مريض يعانون من فرط ضغط الدم الشرياني مع اختلال
شبكية العين الناتج عن فرط ضغط الدم الشرياني. والمجموعتين الجزئيتين متوافقان
مع بعضهما في السن والجنس وكتلة الجسم أيضاً. متوسط ضغط الدم وعلاقته متمايزان
مع المجموعة الضابطة في السن والجسم

أوضح هذه الدراسة ارتفاع مستوي اللبتن بالدم عند مرضى فرط ضغط الدم
الشرياني وعلاقته في المجموعة الجزئية الأولى. والثانية ارتفاعاً ذي دلالات مقارنة
بالمجموعة الأولى الضابطة وأيضًا توجد زيادة ذات دلالة إحصائية في مستوى اللبتن
في المجموعة الجزئية الثانية مقارنة بالمجموعة الجزئية الأولى وقد وجد كذلك ان
هناك علاقة طردية متبادلة بين نسبة اللبتن بالدم ومعدل كتلة الجسم في جميع
المجموعات وأيضًا بين نسبة اللبتن ومتوسط ضغط الدم في جميع المجموعات.