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Original Article

DPP4 activity is related to body weight and central fat in postmenopausal women

Priscila de Oliveira Siciliano [a,*], Amelio F. Godoy-Matos [a], Letícia Dinis da C. Braga [a], José Denise Pires Carvalho [b], José Otávio do Amaral Corrêa [c]

[a] Metabolism Unit, Instituto Estadual de Diabetes e Endocrinologia(IEDE), Rio de Janeiro, RJ, Brazil
[b] Endocrine Physiology Laboratory, Biophysics Institute of Carlos Chagas Filho, Universidade Federal do Rio de Janeiro(UFRJ), Rio de Janeiro, RJ, Brazil
[c] Director of Pharmacy Faculty, Universidade Federal de Juiz de Fora(UFJF), Juiz de Fora, MG, Brazil

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ABSTRACT

Aims: Dipeptidyl peptidase-4 (DPP4) is a new adipokine increased in central obesity and related to insulin resistance (IR). Postmenopausal (PM) state may be associated with increase in body weight and central fat distribution. We hypothesize that DPP4 is increased in PM women.
Materials and methods: Twenty-two non-obese PM and 22 non-obese premenopausal women (PreM), were evaluated. DPP4 activity, lipid profile, HbA1c, FSH, estradiol and sex hormone-binding globulin (SHBG) were measured; an oral glucose tolerance test (OGTT) was performed and IR calculated. Body composition was assessed by dual X-ray absorptiometry (DXA). Correlations between DPP4 and the anthropometric and metabolic variables and body fat distribution were studied.
Results: DPP4 activity was not different between the two groups (PM 5309 ± 650 vs PreM 5387 ± 704 RLU; $p = 0{,}70$). In the PM group there was a significant correlation between DPP4 and body weight ($r = 0{,}498$; $p = 0{,}03$; $n = 22$) and trunk fat ($r = 0{,}477$; $p = 0{,}03$; $n = 21$). There was also a trend for correlation with android ($r = 0{,}418$; $p = 0{,}06$; $n = 21$) and total fat ($r = 0{,}409$; $p = 0{,}06$; $n = 21$). When stratified by BMI, DPP4 was significantly higher in PM women with BMI $\geq 25\ kg/m^2$ ($p = 0{,}02$).
Conclusion: DPP4 was not increased in PM but is associated with body weight and body fat centralization.

1. Introduction

Menopause is a period of significant physiological changes that may be associated with increased body weight and obesity related diseases [1]. In many women attributes of the metabolic syndrome (MS) as insulin resistance (IR), abdominal adiposity, and dyslipidemia appear with estrogen deficiency [2]. Indeed, postmenopausal (PM) status is associated with a 60% increased adjusted risk of the MS. The risk of cardiovascular disease (CVD) attached to the MS seems to be especially higher in women, and it is valued that half of all cardiovascular events in women are associated to the MS [2].

Gaspard [3] and others studies confirmed the observation of an increased prevalence of hyperinsulinemia and IR occurring earlier in non-obese or obese post vs. premenopausal (PreM) women [3–8]. Some other studies have already evaluated the relationship of endogenous sex hormones, mainly androgens, and cardiovascular risk in women [9–11].

Dipeptidyl peptidase-4 (DPP4) is an ubiquitous multifunctional type II transmembrane protease, especially concentrated in adipose tissue, kidneys, T lymphocytes and endothelial cells [12]. Recently, Lamers et al. showed that this enzyme is expressed and released by adipocytes, and correlates positively with body mass index (BMI), adipocyte size and leptin levels and negatively with adiponectin [12]. DPP4 also inhibits the phosphorylation of insulin induced AKT in adipose tissue, skeletal and smooth muscle, what is reversed by the addition of DPP4 inhibitors to the medium. It is also increased in obese, mainly visceral type, what is consistent with a new adipokine linking adipose tissue with MS [12]. Furthermore, Indirect IR markers, such as fasting insulin and HOMA-IR, were positively associated with DPP4 expression in macrophages of visceral adipose tissue [13].

* Corresponding author. Avenida Lúcio Costa 3360, Barra da Tijuca, Rio de Janeiro, 22630-010, RJ, Brazil.
E-mail address: prisiciliano@yahoo.com.br (P.O. Siciliano).

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Therefore, as an adipokine, DPP4 may be increased in PM women and associated with its typical body fat redistribution and metabolic disarrangement. This study aimed to study the plasma activity of DPP4 in PM women and its possible metabolic and anthropometric correlations.

1.1. Subjects, materials and methods

1.1.1. Subjects

Twenty-two PM women and a control group of 22 healthy preM volunteers were recruited through the outpatient clinics of the State Institute of Diabetes and Endocrinology. All participants signed an informed consent form and the study was approved by local ethical committee. Included PM women were non-obese (BMI<30) and non-diabetic, between 3 and 8 years after menopause, without hormonal replacement. Control PreM group had to have regular menses within the last 12 months and did not use contraceptives. Exclusion criteria were BMI<18,5 kg/m2 or >30Kg/m2, weight loss >2 Kg in the last 3 months, use of medications that may interfere with adipose tissue (thiazolidinediones, corticosteroids and others); use of DPP4 inhibitors and incretin mimetics; nursing or planning to be pregnant; acute or chronic renal, hepatic or CVD.

1.2. Anthropometrical examination

All participants were carefully examined by the same investigator. Weight, height, waist circumference (WC), determined at the midpoint between the lowest rib and the iliac crest, hip circumference (HC), obtained by measuring the largest diameter passing through the large trochanters and blood pressure (BP) were measured. BMI was calculated as weight in kilograms divided by the square of height in meters (Kg/m2). WHR was defined by the ratio between WC and HC.

1.3. Laboratory evaluation and procedures

After an overnight fast, venous blood samples were collected to measure fasting plasma glucose (FPG-enzymatic colorimetric method), fasting insulin (electrochemiluminescence), Hemoglobin A1c [HbA1c-High performance liquid chromatography (HPLC)], lipid profile (Enzymatic colorimetric), sex hormone-binding globulin (SHBG), FSH and estradiol (electrochemiluminescence). An oral glucose tolerance test (OGTT-75 g glucose load) was then performed and samples collected at 60 and 120 min to test glucose and insulin concentrations. Plasma DPP4 activity was measured using Promega DPPIV-Glo TM Protease Assay Kits at the biochemistry laboratory of Juiz de Fora Federal University. IR was evaluated by HOMA-IR (homeostasis model assessment) calculated by the formula [Insulin (mU/L) x Glucose (mmol/L)/22.5], Matsuda Index was calculated through a tool contained in the site:http://mmatsuda.diabetes-smc.jp/MIndex.htlm and QUICK(quantitative insulin sensitivity check inbox) calculated by the formula [1/(log insulin + log glucose)].

1.4. Body composition analysis

Dual X-ray absorptiometry (DXA) was done utilizing a LUNAR PRODIGY ADVANCE/GE scan to evaluate body composition.

1.5. Statistical analysis

Statistical analysis was performed using the statistical software SAS System, version 6.11(SAS Institute, Inc., Cary, North Carolina). The descriptive analysis presented the observed data in tables, expressed by mean and standard deviation or median and interquartile range (Q1 and Q3).

The inferential analysis consisted of the following methods: the comparison of clinical, laboratorial and body composition variables between the PM and control groups was evaluated by Student's t-test for independent samples or by the non-parametric test of Mann-Whitney for non-Gaussian variables; and to evaluate the association between the variables in the study with the DPP4, was used the Pearson correlation coefficient or Spearman's non-parametric. Non-parametric methods were applied, since some variables did not present a normal (Gaussian) distribution, according to the rejection of the normality hypothesis by the Shapiro-Wilk test, in at least one of the groups. The level of statistical significance was 5%.

2. Results

Table 1 displays demographic and biochemical results. PM women were older [median age 55 (52–56)] and heavier [median BMI 28,2 (24,2–29,7)]. Glucose was increased in PM women at baseline ($p = 0,003$), 60' ($p = 0,006$) and 120' ($p = 0,024$) and insulin at 60' ($p = 0,006$) and 120' ($p = 0,013$). Accordingly, HOMA-IR was increased and QUICK decreased in PM women who also presented higher HbA1c, TG, VLDL, and systolic and diastolic blood pressure. SHBG was significantly decreased in PM women ($p = 0,0009$). Plasma DPP4 activity was similar between the two groups.

Patients with obesity were not included in this study; however, patients and controls were stratified by BMI <25 or ≥25kg/m2. In the PM women those with BMI ≥25 had significantly greater DPP4 ($p = 0,02$). There was no significant difference in the PreM group ($p = 0,2$).

Regarding body composition, total and android fat were increased in PM (Table 2).

Table 3 demonstrates a significant direct correlation between DPP4 activity, body weight and trunk fat ($r = 0,477$; $p = 0,03$; $n = 21$; and $r = 0,477$; $p = 0,03$; $n = 21$, respectively) as well as with 60′ glucose ($r = 0,498$; $p = 0,02$; $n = 22$) only in the PM group. This means that in the PM group, the higher the weight and trunk fat the higher the expected value of DPP4.

There was a significant correlation between DPP4 with age ($r = 0,484$; $p = 0,02$; $n = 22$) in the control group, and a trend for DPP4 to correlate directly with android ($r = 0,418$; $p = 0,06$; $n = 21$) and total body fat ($r = 0,409$; $p = 0,06$; $n = 21$) in the PM group.

3. Discussion

This study aimed to establish whether DPP4 activity was altered in PM women when compared to a group of PreM. Our results showed no difference and negated the hypothesis, at least in this small and non-obese population. To the best of our knowledge, this is the first study to compare DPP4 between PreM and PM women. Zheng et al. [14] investigated the association between DPP4 activity and osteoporosis in 744 PM women with normal glucose tolerance. They found a strong association between DPP4 activity and the risk of osteoporosis and its pathogenic factors such as IR, inflammation and decreased levels of active GLP-1. In their study, patients with higher levels of DPP4 exhibited higher BMI, TG, total cholesterol, fasting insulin, HOMA-IR, IL-6, high sensitivity CRP and lower levels of active GLP-1 [14].

In this study, although there was no difference between the groups, DPP4 exhibited a positive correlation with weight and trunk fat in PM group. Accordingly, there was a tendency to correlate with android fat and total body fat but not with BMI, only in PM women. It should be considered that in some way our data

Table 1
Clinical and biochemical variables in a sample of post-menopausal (PM) in comparison to pre-menopausal (PreM) women groups.

Variable	PM(n = 22)				PreM(n = 22)				*p value*
Age (years) [b]	55,0	52,0	–	56,0	43,0	38,8	–	47,0	< **0,0001**
Weight (kg) [b]	69,9	57,1	–	75,6	62,7	58,6	–	68,0	0,091
BMI (kg/m[b])	28,2	24,2	–	29,7	25,2	23,0	–	26,9	**0,034**
SBP (mmHg) [b]	125,0	114,5	–	130,0	110,0	100,0	–	130,0	**0,018**
DBP (mmHg) [b]	80,0	70,0	–	80,0	70,0	60,0	–	80,0	**0,022**
Basal glucose (mg/dl) [b]	87,0	83,0	–	101,3	79,0	73,0	–	82,3	**0,003**
Glucose 60' (mg/dl) [b]	135,0	107,0	–	151,8	95,0	85,3	–	135,0	**0,006**
Glucose 120' (mg/dl) [b]	109,5	96,8	–	133,0	92,5	82,5	–	111,8	**0,024**
Insulin 60' (mcU/mL) [b]	64,7	44,0	–	116,0	30,9	23,5	–	78,7	**0,006**
Insulin 120' (mcU/mL) [b]	56,2	34,7	–	86,9	26,8	15,3	–	45,8	**0,013**
HbA1c (%) [a]		5,57	±	0,40		5,21	±	0,40	**0,004**
Homa IR [b]	1,99	1,53	–	2,38	1,00	0,86	–	2,00	**0,016**
TG (mg/dl) [b]	114	87	–	153	80	54	–	102	**0,001**
VLDL (mg/dl) [b]	22,5	17,5	–	30,5	16,0	10,8	–	20,0	**0,002**
SHBG (mmol/L) [b]	50,5	38,8	–	61,0	82,0	52,5	–	102,3	**0,0009**
DPP4 (RLU) [a]		5309	±	650		5387	±	704	0,70

BMI body mass index *SBP* systolic blood pressure *DBP* diastolic blood pressure *Homa IR* homeostasis model assessment insulin resistance *TG* triglycerides *VLDL* very low-density lipoprotein *SHBG* sex hormone-binding globulin *DPP4* dipeptidyl peptidase-4.
[a] Variables expressed by mean ± standard deviation and compared by Student's t-test for independent samples.
[b] Variables without a normal distribution expressed by median and interquartile range (Q1 - Q3) and compared by the non-parametric test of Mann-Whitney.

Table 2
Measures of body composition from post-menopausal (PM) and pre-menopausal (PreM) women.

Variable	PM(n = 21)			PreM(N = 21)			*p value*
Android fat (%)	47,6	±	7,0	41,5	±	8,2	**0,013**
Gynoid fat (%)	50,1	±	5,8	47,1	±	5,3	0,086
Trunk fat (%)	44,0	±	7,6	39,6	±	6,7	0,055
Total body fat (%)	43,3	±	6,6	39,2	±	5,6	**0,034**
Android/gynoid fat ratio	0,953	±	0,105	0882	±	0,143	0072
Fat mass ratio (FMR)	0,965	±	0,126	0936	±	0,108	0,43

Variable expressed by mean ± standard deviation and compared by Student's t-test for independent samples.

are in agreement with Zheng's et al., at least in relation to the anthropometric variables. Different from the present study, in the study of Zheng et al. the mean age was 59,5 years (47–76) and it was observed that women with higher DPP4 were more likely to be older and consequently more related to the IR markers. In this study, DPP4 was related to age only in the PreM women but the mean age of PM women was 54,3 years (50–58), what may explain why our results did not match to Zheng's.

Although women with obesity were not included, dividing the two groups between those with a BMI<25 and BMI ≥25, we observed a higher DPP4 in the overweight band of this group. This suggests that, after menopause, even with a small increase in weight and more central fat distribution, the activity of this adipokine tends to increase. Such observation highlights one of the limitations in this study, because we did not include participants with a BMI ≥30. Indeed, in the study by Lamers et al. [12], serum concentrations of DPP4 were increased in obese individuals and correlated with BMI, adipocyte size in subcutaneous and visceral fat and adipocyte hormones adiponectin (negatively) and leptin. In addition, the current study measured the activity and not the concentration of DPP4. Therefore, it is possible that the activity of the enzyme does not reflect in the same way as the plasma concentration a greater production by the adipose tissue [12].

It is very difficult to part the effects of normal aging from the hormonal effects of PM. Cross-sectional [15] and longitudinal studies [16,17] have shown an association between the menopausal transition and increased abdominal adiposity, regardless of the age

Table 3
Correlation between DPP4 activity with clinical, laboratory and body composition variables in the total sample and in the post-menopausal (PM) and pre-menopausal (PreM) groups.

Variable	Total sample (n = 44)		PM group (n = 22)		PreM group (n = 22)	
	r	*p value*	r	*p value*	r	*p value*
Age[b]	0,017	0,91	−0,089	0,69	0,484	**0023**
Weight[b]	0,258	0090	0,449	**0036**	0,148	0,51
BMI (kg/m[b])	0,199	0,20	0,191	0,40	0,163	0,47
Basal glucose[b]	0,144	0,35	0,406	*0061*	−0,150	0,50
Glucose 60' [b]	0,281	*0065*	0,498	**0018**	0,233	0,30
Glucose 120' [b]	0,196	0,20	0,129	0,57	0,322	0,14
Basal insulin [b]	0,160	0,30	−0,145	0,52	0,359	0,10
Insulin 60' [b]	0,063	0,69	0,055	0,81	0,115	0,61
Insulin 120' [b]	0,011	0,94	−0,172	0,44	0,362	*0098*
Android fat (%) [a]	0,098	0,54	0,418	*0059*	−0,028	0,90
Gynoid fat (%) [a]	−0,019	0,91	0,330	0,14	−0,271	0,24
Trunkal fat (%) [a]	0,122	0,44	0,477	**0029**	−0,121	0,60
Total body fat (%) [a]	0,064	0,69	0,409	*0065*	−0,183	0,43
Android/gynoid fat ratio [a]	0,121	0,45	0,179	0,44	0,154	0,50
Fat mass ratio (FMR) [a]	0,182	0,25	0,338	0,13	0,071	0,76

BMI body mass index.
[a] Pearson correlation coefficient. PM(n = 21); PreM(n = 21).
[b] Spearman's non-parametric correlation coefficient for variables without a normal distribution.

effect and total body adiposity [2]. In the present study, PM women have increased android and total body fat. Valerio et al. [18,19] have demonstrated that central to peripheral fat ratio as measured by FMR may be useful to investigate fat distribution in patients with generalized and partial lipodystrophy, however in this study there was no difference between the preM and PM women. In agreement with the body composition findings, some metabolic parameters such as fasting, 60′ and 120′ glucose, HbA1c, TG and HOMA-IR revealed a worse metabolic pattern in PM women. In addition, SHBG was significantly lower in PM women than in preM women.

Studies carried out by dosing other adipokines in PM have demonstrated diverse results. Khokhar et al. [20] found higher levels of leptin in PreM women and suggested that lower levels of leptin may be attributed to postmenopausal status. Priya et al. [21] observed that although previous studies [22,23] reported higher production of leptin in PreM women, their data did not confirm these observations. Instead, leptin levels were significantly increased and related to body weight but not to climacteric.

Other important adipokine, adiponectin, increases with age what has been attributed to a decrease in kidney adiponectin clearance ([24,25]). However, menopausal status may also interfere [26,27]. Gavrila et al. [26] found significantly higher adiponectin levels in PM women. Koh et al. [27] also reported that adiponectin levels are significantly higher in older women (>40 years), despite the visceral fat area increase with age.

As discussed earlier, serum concentrations of DPP4 is increased in obese, mainly in those with increased visceral fat [12]. More importantly, DPP4 correlates to adiponectin levels (negatively), and leptin levels (positively). Unfortunately we did not measure those adipokines, but the DPP4 relationship with trunk fat and with some markers of insulin resistance in this study suggests that a larger study may clear some of these points.

In conclusion, DPP4 activity is not increased in PM women within a limited BMI category compared to PreM women. It is, however, associated with some markers of body fat centralization and weight gain. Larger studies in PM, including obese women are warranted.

Conflicts of interest

The authors declare that they have no conflict of interest.

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