Lipid and Glucose Metabolism Biomarkers in Non-Diabetic Hemodialysis and Peritoneal Dialysis Patients

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Abstract: Background: Chronic kidney disease is well established risk factor for cardiovascular disease, because of multifactors such as disturbance of mineral metabolism, fluid over load, insulin resistance, and disturbance of carbohydrates and lipid metabolism, these factors are not totally corrected by initiation of dialysis, even though peritoneal dialysis may add further risk due to great glucose absorption from peritoneal dialysis fluids. The aim of our study is to compare the biomarker of carbohydrate and lipid metabolism in non diabetic peritoneal and hemodialysis patients and its impact on cardiovascular system. Patient and method: Forty patients with end stage renal disease treated with HD or PD for more than six months. The PD patients were using glucose- based solution. blood concentration of insulin, glucose, glycosated hemoglobin, total cholesterol, triglycerides, HDL-c, LDL-c, albumin, intact PTH, calcium, phosphorus, hemoglobin and serum homocysteine level were measured, homeostasis model assessment index was calculated and. Carotid Doppler was performed and measured carotid intima media thickness was used as a sign of early atherosclerosis. Results: Forty patients (55 % males, mean age 42±15), 25 were on HD and 15 on PD. There were significant high systolic blood pressure in HD patients ($p<0.01$). Albumin level was significantly higher in HD group ($p<0.01$). Also S.P was higher in HD patients ($p<0.01$),serum homocysteine level was higher in HD patients ($p<0.05$) and a significantly higher m-CIMT ($p<0.01$) in HD patients with no significant difference between the two groups in SCa, intact PTH and hemoglobin, PD patients have a significant higher level of fasting glucose ($p<0.05$). HbA1c ($p<0.05$), also higher fasting insulin is observed in PD patients ($p<0.05$), also PD patients had significant lower insulin sensitivity HOMA index ($p<0.05$), also cholesterol was significantly higher in PD patients ($p<0.01$), also LDL-c was higher in PD patients ($p<0.01$), HDL-c was higher in PD patients ($p<0.01$), triglycerides also were significantly higher in PD patients ($p<0.05$). Conclusion: PD patients have a worse profile of lipid and glucose metabolism than HD patients, however there is an increased risk of atherosclerosis in HD patients due to more inflammatory process induced by HD. PD could be safer if measure was taken to reduce the glucose load including the use of glucose sparing solution.

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1. Introduction

Carbohydrate metabolism disturbances are known factors potentially associated with cardiovascular complications in patients with chronic kidney disease (CKD). Disorders of lipids and glucose metabolism are commonly found in the early stages of CKD and aggravate with the progression of kidney dysfunction. Recent reports suggest that the relationship between hyperglycemia and cardiovascular disease (CVD) may extend below the limits currently defined as diabetes, since higher levels of glycosylated hemoglobin (HbA1c) are independent predictors of mortality in general population and non-diabetic CKD patients.(1)

Insulin resistance was also identified as an independent predictor of cardiovascular events and mortality in general and CKD patients (2).

The initiation of peritoneal dialysis (PD) represents an additional risk to glucose metabolism, due to the absorption of dextrose contained in the dialysate, which potentially intensifies carbohydrate disturbances (3).

In fact, patients with no previous history of glucose intolerance are more likely to develop hyperglycemia and *de novo* diabetes after the initiation of PD therapy, as described in previous studies (4,5).

Such high glucose load offered during PD therapy can also contribute to insulin resistance and worsening of dyslipidemia. However, specific factors are also introduced when hemodialysis (HD) is initiated. Information comparing the prevalence of these metabolic disturbances in unselected PD and HD patients is important to provide substrate for future actions.

Thus, the aim of this study was to compare biomarkers of carbohydrate and lipid metabolism in non-diabetic PD and HD patients and its impact on cardiovascular system.

2. Patients and Methods

This study was carried out at nephrology unit,

Zagazig university hospital from Jan 2009 till may 2011 included forty non diabetic adult patients with end-stage renal disease treated with HD or PD (on therapy for more than 6 months). All PD patients were dialyzed with glucose-based solutions.

A blood sample was taken from all patients in the morning after overnight fasting. Serum concentrations of insulin, glucose, triglycerides, total cholesterol, HDL-c, LDL-c, albumin, intact PTH, calcium, phosphorous, C-reactive protein (CRP) and hemoglobin were measured.

Insulin and intact PTH were determined by Immulite®, DPC US, it is a solid phase chemiluminescent enzyme labeled immunoassay. Levels of total cholesterol, HDL-C and triglycerides were measured while LDL-C was calculated.

CRP was measured using an immunonephelometric method on a BN ProSpec System with commercial kits (Dade Behring).

The homeostasis model assessment (HOMA) index was then calculated using the baseline insulin and glucose concentrations: HOMA = (FPG × FPI)/22.5; FPG = fasting plasma glucose (mmol/L); FPI = fasting plasma insulin (mU/mL).(4)

Serum homocysteine was determined by chemiluminescent assay using commercial kits on Immulite ®, DPC US. A fasting HMC concentration above 15 µmol/L is the most common definition of hyperhomocysteinemia (6).

Carotid Doppler examination was performed using an echocardiographic system (model 5000; Advanced Technology Laboratories, Bothell, WA, USA) equipped with a variable (2–4 MHz) phased array, cross-sectional transducer, and harmonic imaging. The common carotid arteries bilaterally were scanned in all patients. The far wall of the common carotid artery, 0.5–1 cm proximal to the beginning of the carotid bulb, was used for carotid artery intima media thickness (CIMT) measurement. CIMT was measured as the distance between the leading edge of lumen-intima echo and media-adventitia echo as defined previously. CIMT were measured during end-diastole. The average of both side CIMT measurements was considered as mean-CIMT. The number of atherosclerotic plaques (soft plaque = grey echo, calcified plaques = white echo) were recorded. All carotid artery measurements were performed in plaque free arterial segments. M-CIMT >1 mm was defined as atherosclerosis.(7)

Blood pressure was measured with a standard mercury sphygmomanometer by the auscultator method and after a 20-minute rest period in supine position. Pulse pressure was calculated as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Abdominal waist circumference was assessed in PD patients after a complete drainage of dialysis solution from the peritoneal cavity.

Statistical analyses:

Data were expressed as mean ± SD for quantitative variables, t-test and pearson correlation were used for analysis of result. p value <0.05 was considered significant. All analyses were performed with SPSS statistical package version 10 (SPSS Inc., Chicago, IL).

3. Results

Characteristics of study population

Forty patients (55% males, mean age 42 ± 15 years), 15 were on PD and 25 on HD. PD patients were older (44 ±11 *versus* 41 ± 9 years; *p* =NS) and HD patients were on dialysis for longer periods (31 ± 10 *versus* 30 ± 8 months; *p* = NS).

There was a trend to PD patients to have higher abdominal waist circumference (93.3 ± 12.8 *versus* 87.5 ± 12.1 cm; *p* = NS), which was taken after a complete drainage of dialysis solution from the peritoneal cavity, while body mass index (BMI) was slightly, but with no statistical difference, lower in HD patients (26.6 ± 4.8 *versus* 27.3±3.8 kg/m^2; *p* = NS).

There was no significant difference regarding underlying renal disease. Although there was no statistical difference in diastolic blood pressure, the significant higher (p<0.01) systolic blood pressure observed in HD patients (148 ± 17 *versus* 133 ± 30 mmHg) lead to a higher pulse pressure in these patients (65.5 ± 11.8 *versus* 51.6 ± 15.1 mmHg;(*p* < 0.01). Demographic and clinical variables of the study population are shown in (Table 1)

General biochemical characteristics

Hemoglobin levels were very similar between groups (11.8 ± 1.6 *versus* 11.9 ± 2.0 g/ml; *p* = NS). Albumin levels were significant higher *(p* < 0.01) in HD group (4 ± 0.46 *versus* 3.6 ± 0.5 g/dL) HD patients presented higher levels *(p* < 0.01) of serum Phosphorus (6.1±2 *versus* 4.4 ± 1.0 mg/dl) and a tendency to more elevated iPTH levels (471 ± 584 *versus* 281 ± 348 pg/L; *p* = 0.07). There was no difference in total calcium serum levels (9.2 ± 1.2 *versus* 9.2 ± 0.68 mg/dl; *p* = 0.98).(Table 2)

Carbohydrate metabolism biomarkers

PD patients presented significant higher fasting glucose levels (90 ± 2.52 *versus* 82.44 ± 2.52 mgl/dl; *p* < 0.05) and HbA1c (5.9 ± 0.1 *versus* 5.5 ± 0.1%; *p* < 0.05).

There was a trend to higher fasting insulin levels in PD patients (97.9 ± 12.8 *versus* 57.9 ± 12.3

pmol/L; $p < 0.05$).

Importantly, PD patients presented significant lower insulin sensitivity: HOMA index was almost twice higher (3.27 *versus* 1.68; $p < 0.05$).(Fig 1) and (Table 3)

Table (1): Demographic and clinical variables of the study population (M± SD)

PARAMETER	HD patients	PD patients	P VALUE
Age (yrs)	41±9	44±11	NS
BMI (kg/m^2)	26.6±4.8	27.3±3.8	NS
Duration of dialysis(months)	31±10	30±8	NS
Abdominal waist circumference (cm)	87±12.1	93.3±12.8	NS
Systolic blood pressure (mmHg)	148±17	133±30	<0.01

Table (2) : General biochemical characteristics(M± SD)

PARAMETER	HD patients	PD patients	P VALUE
Hemoglobin (mg/dl)	11.8±1.6	11.9±2	NS
Albumin (mg/dl)	4±0.46	3.6±0.5	<0.01
Phosprous (mg/dl)	6.1±2	4.4±1	<0.01
iPTH	471±155	281±130	0.07
Ca (mg/dl)	9.2±1.2	9±0.68	NS

Table (3) : Carbohydrate metabolism biomarkers (M± SD)

PARAMETER	HD patients	PD patients	P VALUE
Fasting glucose (mg/dl)	82.44±2.52	90±2.52	<0.05
HbAc1 %	5.5±0.1	5.9±0.1	<0.05
Insulin (pmol/l)	57.9±12.3	97.9±12.8	<0.05
HOMA-IR	3.27±0.6	1.68±0.4	<0.05

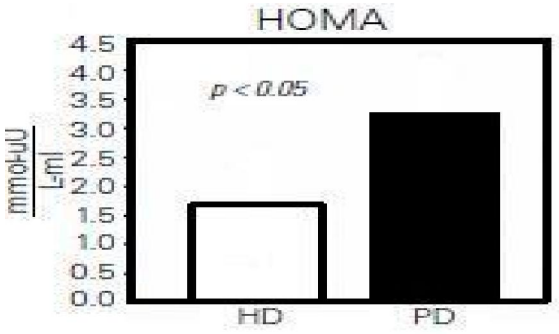

Fig (1)

Lipid metabolism biomarkers

Total cholesterol (230 ± 38.7 *versus* 182 ± 43.8 mg/dl) and LDL-c (137.5 ± 32.8 *versus* 90.5 ± 32.1 mg/dl) were significant higher ($p < 0.01$) in PD patients.

Hypertriglyceridemia (>200 mg/dl) was present in50% of all patients of which67% in PD and 40% of HD patients. These triglycerides levels were significantly higher (p<0.05) in PD patients than HD patients (245 ± 120.8 *versus* 164.38 ± 61.5 mg/dl).

LDL-c were significantly higher (p<0.01) in PD patients than in HD patients (137.5±32.8 mg/dl versus 90.5±32.1 mg/dl). Also HDL-c were significantly higher (p<0.01) in PD patients than HD patients (43±15 mg/dl versus 32.3±9).

Insulin sensitivity tests were moderately correlated to BMI (r = 0.48; p <0.01), abdominal waist circumference (r = 0.51; $p < 0.01$), total cholesterol (r = 0.33; p <0.05) and triglycerides (r =0.59; $p < 0.01$).

Serum homocysteine level and m-CIMT were used to evaluate atherosclerosis. The presence of carotid artery plaques was also assessed.

In five HD patients (20%), atherosclerotic plaques were found (in three patients at both carotid arteries, in two patients at only the left side) and in four PD patients (26%), atherosclerotic plaques were found (in two patients at both carotid arteries, in one patient at the left side, and in one patient at the right side).

Rate of patients with atherosclerotic plaque was similar in both groups (P = NS). Patients who had carotid plaque had higher serum CRP levels as compared to patients without carotid plaque (20.1 ± 5.6 mg/l vs. 12.0 ± 3.3 mg/l, p<0.05).

Serum homocysteine level was higher in HD patients than PD patients (28 ± 3.2 µmol/L vs. 16.1 ± 6.9 µmol/L, P = 0.05). Twenty patients (80%) in the HD group and 10 patients (67%) in the PD group were hyperhomocysteinemia.

Increased m-CIMT is accepted as a sign of early atherosclerosis. In this study, we found that m-CIMT was higher in HD patients than PD patients, despite PD patients having a more atherogenic lipid profile (1.18 ± 0.16 mm vs. 1.06 ± 0.13 mm, P < 0.01).

Table (4): Lipid metabolism & atherosclerosis biomarkers (M± SD)

PARAMETER	HD patients	PD patients	P VALUE
Total cholesterol (mg/dl)	182±43.8	230±38.7	<0.01
Triglycerides (mg/dl)	164.38±61.5	245±120.8	0.05
LDL-C (mg/dl)	90.5±32.1	137.5±32.8	<0.01
HDL-C (mg/dl)	32.3±9	43±15	<0.01
CRP (mg/dl)	18±2.9	21.5±3.5	NS
Homocysteine(µmol/L)	28 ± 3.2	16.1 ± 6.9	0.05
m-CIMT (mm)	1.18±0.16	1.06±0.13	<0.01

4. Discussion

Carbohydrate disturbances are common findings in CKD even in the early stages. The progressive decline of renal function intensifies CKD-related risk factors such as mineral metabolism disturbances, fluid overload, anemia, uremic toxins and worsening of insulin resistance, dyslipidemia and increased signs of oxidative stress and inflammation.(8)

Its known that initiation of dialysis therapy partially revert those disturbances.(9) However, initiation of PD adds potential harm related to the great glucose absorption from PD fluids that lead to worsening of insulin resistance, dyslipidemia and higher levels of HbA1c. In the present study we confirm that the glucose and lipid metabolism profile in PD patients is worse than the observed in their HD counterparts.

A fasting state condition is difficult to achieve in most PD patients in consequence of the continuous glucose absorption from dialysate.(4).

In this study, PD patients presented significant higher levels of oral fasting glucose compared to HD patients. This elevation was confirmed with a higher HbA1c levels observed in the PD group: 5.9% higher than HD patients' levels.

This may represent potential harm to PD patients, since HbA1c has been strongly associated with a high risk for diabetes, CV disease and all cause mortality in general non-diabetic patients and CKD patients.(10)

Although HbA1c it's not considered the ideal method to evaluate glycemic control in the uremic setting, it is still widely available and can be an useful tool to compare groups and stratify those at high risk. Its ideal levels are still not established.(11)

Moreover, hyperlipidemia, a well-known risk factor for CVD in general population, is very common in CKD and can be found in up to 50% of end stage renal disease (ESRD) patients.(12)

The causes of these lipid disorders are multifactorial and have been already associated with genetic factors, diet, obesity, CKD itself, dialysis solution, insulin resistance and inflammation. Recently, a randomized clinical trial with more than 9,000 CKD patients, of which 3,000 on dialysis, showed better outcomes after treatment of dyslipidemia.(13)

PD patients presents a high prevalence of dyslipidemia probably related to the high glucose load absorbed from peritoneal cavity every day. In this study, PD patients presented significant higher levels of TC, LDL-c and HDL-C. TG was also significantly higher. Except for the significant higher HDL levels in PD patients, our data are similar of those found by Siamopoulos *et al*. in which PD patients presents a worsened lipid profiles.(14)

Hypertriglyceridemia is the most common lipid disorder in PD patients and was found in almost67% of our PD patients. It has been related to IR in non-diabetic, non-obese patients undergoing PD almost 10 years ago. (15)

The mechanisms postulated to be involved with dyslipidemia and IR in PD patients are increased hepatic synthesis of VLDL due the hyperinsulinemia caused by the high glucose absorption from peritoneal cavity, decreased removal of TG in consequence of a impaired regulation of lipoprotein lipase activity by insulin, peritoneal protein loss and weight gain. (16, 17)

In a large prospective cohort study of 15,632 women aged 45 or older, the total cholesterol/HDL-c ratio has been suggested as a predictor as good or better than apolipoproteins fractions for prediction future cardiovascular events (15) while McLaughlin *et al*. reported triglycerides/HDL-c ratio as a reliable

indicator of insulin resistance(18).

Although not yet validated in CKD patients, we compared these lipid ratios between PD and HD patients controlling them for covariates and a significant increase was found in PD patients in line with the mentioned studies. The ratio was almost 50% higher when TC/HDL ratio was considered and 75% with LDL/HDL ratio.

Insulin resistance, which is also considered a risk factor for CVD, was recently associated with all-cause mortality even in a large cohort of 5511 non-diabetic patients (2) and is commonly found in CKD patients, even during their early stages.(19)

Insulin sensitivity was lower in our PD patients as in HOMA index and triglycerides/HDL-c ratio. The mechanism involved is probably related to the higher glucose load daily offered to PD patients, which leads to a high fasting glucose and a compensatory hyperinsulinemia.

When considering serum CRP levels, HD seems to be similar to PD for inflammation. Mean-carotid artery intima media thickness measured with carotid Doppler examination is used as a non-invasive method to evaluate atherosclerosis.

In autopsy study, a close correlation between coronary artery atherosclerosis and extent of atherosclerotic lesions in the carotid arteries has been revealed.(20)

In a study by Hodis et al., it was concluded that the absolute intima-media thickness and the progression of intima-media thickness predicted risk for coronary events beyond that predicted by coronary arterial measures of atherosclerosis and lipid parameters.(21)

In the present study, in spite of having more atherogenic lipid profile, m-CIMT was lower in PD patients than HD patients, but serum homocysteine level was higher in HD patients. Likewise, in a study by Zoccali et al., it was reported that HD patients have a higher fibrinogen level and increased m-CIMT than PD patients and serum homocysteine level was similar between both groups. In the same study, they reported increased prevalence of carotid artery plaque as the serum CRP level increased.(22)

We also found that patients with atherosclerotic carotid artery plaque had higher CRP levels than patients without plaque. Prevalence of carotid artery plaque has been reported as high as 72% in predialytic ESRD patients.(23)

Carotid plaque prevalence in our study was lower (22.5%) probably due to younger patients and lower time on dialysis in the study group. In terms of atherosclerosis, PD treatment is superior, as compared to HD treatment.

Because hyperhomocysteinemia is an independent risk factor for development of atherosclerotic cardiovascular disease in the non-uremic population, it has received considerable attention in the last two decades.

An elevated homocysteine level was detected in most of ESRD patients and correlated with the presence of vascular disease. The relationship between hyperhomocysteinemia and premature atherosclerosis is not well understood. Most studies suggest that homocysteine may enhance lipoprotein oxidation, increase smooth muscle cell proliferation, induce endothelial activation of factor V, and reduce protein C activation by arterial and venous endothelial cells. It is now well-established that uremic patients have a high prevalence (84–92%) of hyperhomocysteinemia.(24)

However, there are a few reports on comparing homocysteine levels between HD and PD patients. Moustapha et al., investigated serum homocysteine levels and the prevalence of hyperhomocysteinemia in both HD and PD patients. They reported HD patients had a higher ($P = 0.001$) homocysteine level than PD patients (29.8 µmol/L vs. 19.9 µmol/L,).(25)

Also, prevalence of hyperhomocysteinemia in HD patients was higher than PD patients (23). Consistent with this report, we also found higher ($P = 0.05$) serum homocysteine levels in HD patients versus PD patients (28 ± 3.2 µmol/L vs. 16.1 ± 6.9 µmol/L).

In many studies, hyperhomocysteinemia is shown as a risk factor for atherosclerosis and association between hyperhomocysteinemia and m-CIMT was defined.(26, 27)

Mallamaci *et al.*, reported that hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients.(28)

Zoccali *et al.*, showed positive correlation between CIMT, serum homocysteine level, and time on dialysis.(22)

Additionally, it was reported that serum homocysteine level was an independent predictor of both m-CIMT and presence of atherosclerotic plaque. Consistent with these results, we also found serum homocysteine level as an independent predictor of m-CIMT.

Libetta *et al.*, showed the strong correlation between plasma homocysteine and m-CIMT, and this correlation emphasizes the role of hyperhomocysteinemia as a major risk factor for atherosclerosis. (29)

However, it was reported that dialysis patients with cardiovascular disease had lower plasma homocysteine levels, as well as a greater prevalence of malnutrition and hypoalbuminemia, than those without cardiovascular diseases. (30)

The use of glucose sparing solutions is an interesting approach aiming to reduce glucose load

and by consequence IR. Amici *et al*., in a cross-sectional study of non-diabetic PD patients treated with either icodextrina 7.5% during the long dwell or the traditional prescription with glucose, firstly described a metabolic advantage in the former, with a reduction in hyperinsulinism and IR measured by HOMA index. (31)

In addition to the reduction in glucose load Takeguchi *et al*. described an increase I adiponectin serum levels with icodextrin in 25 prevalent PD patients, an important factor for increasing insulin sensitivity.(32)

Conclusion:

Both dialysis modalities increase the risk of atherosclerosis with higher risk in hemodialysis in-spite of a worst profile of lipid and glucose metabolism in PD patients. Peritoneal dialysis could be safer if therapeutic strategies, such as pharmacological interventions and/or the reduction in glucose load including the use of glucose sparing solutions aiming to reduce morbidity and mortality in the PD population.

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