Determination the Effect of Glucose on BTP, LFABP Levels in the Patients with Diabetic Nephropathy

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تحديد تأثير الكلوكوز في مستويات BTP و LFABP في مرضى اعتلال الكلى السكري

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Abstract

Everywhere in the globe, kidney illness is becoming more common, and there is no medication that can stop the progression of chronic kidney disease to end-stage renal disease, which is extremely expensive. Diabetes, kidney stones, accidents, and bleeding are the main contributors to kidney disease. The study was designed as a case control study. The study was involved (80) participants, only (36) were involved in this study and divided into two groups patients with nephropathy (23) and diabetic nephropathy (13) with age (20-65years) and BMI (19 -29 kg/m2) .All these patients were diagnosed by nephrologist conducted in nephrology Clinic at al-Emma al Sadeq Hospital and AL Hila teaching hospital in Hila city and Department of biochemistry in Collage of Medicine at University of Babylon from October 2022 to March 2023. In current study measured the glucose ,urea ,creatinine ,GFR ,BTP ,LFABP , salivary hydroxyl and amide bands .The glucose ,urea and creatinine measured by caloric spectrophotometry (CECIL CE2021) ,the BTP and LFABP measured by Elisa (biotekELx50) also salivary hydroxyl and amide bands measured by FT-IR (Bruker) Tensor27. The study showed non-significant differences for (age, and BMI) between patients with nephropathy and diabetic nephropathy. Also in the current study the result show a significant differences of glucose , creatinine and GFR and a non- significant of urea . On the other hand the result show non-significant increase of BTP ,LFABP and salivary hydroxyl and amide bands between studied groups . In conclusion, the BTP and LFABP are linked with GFR and are thought to be indicated presence of renal impairment regardless of glucose effect.

Keywords: Nephropathy (NP), Diabetic nephropathy (DNP), Beta trace binding protein(BTP), Liver fatty acid binding protein(L-FABP), Salivary hydroxyl and amide.

المستخلص

أصبحت أمراض الكلى أكثر شيوعًا ، ولا يوجد دواء يمكن أن يوقف تطور مرض الكلى المزمن إلى المرحلة النهائية من مرض الكلى ، وهو مكلف للغاية. يعد مرض السكري وحصوات الكلى والحوادث والنزيف من العوامل الرئيسية المساهمة في أمراض الكلى، صممت الدراسة الحالية كدراسة حالة اشتملت على 80 مشاركا وجد منهم (36) مشاركاً مصابين بامراض الكلى قسموا الى مجموعتين (23) مصابا باعتلال الكلى و(13) مصابا باعتلال الكلى السكري بعمر (25-63 سنة) ومؤشر كتلة الجسم (19-29 كغ / م 2)، وشخص جميع هؤلاء المرضى والاشخاص الطبيعيين من قبل أخصائي أمراض الكلى. عيادة أمراض الكلى بمستشفى الامام الصادق ومستشفى الحلة التعليمي في مدينة الحلة وقسم الكيمياء الحيوية في كلية الطب بجامعة بابل من 2022/1/9 إلى2022/1/11. في الدراسة الحالية قيس الكلوكوز واليوريا والكرياتنين ومعامل الترشيح الكبيبي وكذلك BTP و LFAB و hydroxyl bands, amide bands الموجودين في اللعاب. قيس الكلوكوز واليوريا والكرياتنين بواسطه CECIL و ال BTP, LFABP بواسطه ال ELISA وكذلك amide band وhydroxyl bands بواسطه FT-IRوقد أظهرت الدراسة فروقًا غير معنوية لــ (العمر ، ومؤشر كتلة الجسم) بين المرضى الذين يعانون من اعتلال الكلية واعتلال الكلية السكري. كما أظهرت النتائج في الدراسة الحالية وجود علاقه معنويه بالكلوكوز والكرياتين وGFR ولا يوجد علاقه لليوريا بين المجموعتين ,ومن ناحيه اخرى أظهرت النتائج الى وجود زياده غير معنويه BTP و LFABP وكذلك نقصان غير معنوي لحزمتي hydroxyl وamide الموجودة في اللعاب بين المجموعات المدروسة . في الختام، يرتبط BTP و LFABP بــ GFR ويُعتقد انهما مؤشر إلى وجود اعتلال كلوي بغض النظر عن تأثير الجلوكوز.

الكلمات المفتاحية: الكلوكوز، مرضى اعتلال الكلى و الكبد

Introduction

Nephropathy is a word used in medicine to describe kidney illness or injury that can lead to renal failure. Loss of kidney function is a potentially lethal ailment since the kidney's main and most evident activities are to manage the body's water and acid-base balance and eliminate any waste products [Calle, *et al*.,2020] . The incidence of diabetes is rising globally, particularly due to the rise in type 2 diabetes. Up to 40% of diabetic people get diabetic nephropathy, which is the main cause of end-stage renal disease. Diabetic nephropathy develops and worsens as a result of several reasons. The etiology of diabetic nephropathy is significantly influenced by oxidative stress, which is increased by hyperglycemia and leads to an increase in free radical generation. Free radicals are challenging to quantify and have a short half-life. However, oxidation products such as lipid peroxidation, protein oxidation, and nucleic acid oxidation have longer half-lives and are used to assess oxidative stress. Numerous oxidative stress indicators connected to diabetic nephropathy have been discovered in recent years.[Jaswal, et al., 2022][Vodošek Hojs, *et al*., 2020].

The major cause of chronic kidney disease among patients beginning renal replacement treatment is diabetic nephropathy, which is also linked to an elevated risk of cardiovascular death. Proteinuria >0.5 g/24 h has traditionally been used to identify diabetic nephropathy. Overt nephropathy, clinical nephropathy, proteinuria, and microalbuminuria are among terms used to describe this stage [Gross, *et al*., 2005] . .

Saliva is a bio fluid of clinical importance that is simple to collect, easy to store, and has been shown to be optimal for detecting systemic disorders early. Saliva is a source of a variety of biomarkers, and it may be utilized in

point-of-care (POC) devices, quick diagnostics, and other common clinical laboratory procedures.[Shakeeb, *et al*., 2021]stress-free, and preferable diagnostic material than blood. Supporting evidences acknowledge saliva as a mirror that reflects the body's physical state. Numerous studies have also demonstrated the presence and use of RNA derived from saliva in the early diagnosis of disease by real-time reverse transcriptase polymerase chain reaction (RT-PCR. The use of saliva for the diagnosis of kidney disease (KD) through infrared spectroscopy is an emerging research area in clinical diagnostics. Infrared spectroscopy is a non-invasive technique that detects changes in the chemical composition of biological samples based on the unique spectral fingerprint of their molecular vibrations[Campanella, *et al*., 2023] .

The recent discovered marker that can be recognized beta trace binding protein (BTP) and liver fatty acid binding protein(L-FAPB), BTP originating from kidneys, genital organs, heart, resorption of cerebrospinal fluid, the liver eliminates highest concentration of (BTP).

BTP molecules with smaller carbohydrate residues were identified in cerebrospinal fluid, making them a signal for differentiating cerebrospinal fluid leak from other physiological fluids [den Bakker, *et al*., 2018]this invasive and cumbersome technique is not widely available and GFR is commonly estimated using serum levels of endogenous markers. Creatinine, urea, cystatin C, beta-trace protein, and beta-2 microglobulin are well-established endogenous markers of kidney function. These markers differ in site of production and effects of diet and medication, as well as renal-tubular handling and extra-renal elimination. For each marker, different methods are available for measurement. Importantly, the measurements of creatinine and cystatin C have recently been standardized with the introduction of

international reference standards. In order to allow estimation of GFR from serum marker concentrations, different equations for estimated GFR (eGFR, bringing the molecular weight range of BTP in serum down to 26-29 KD. Also BTP is not physiologically inert. It has ligand-binding and enzymatic characteristics. Prostaglandin H2 (PGH2) is converted to prostaglandin D2 (PGD2) by BTP. A number of crucial physiological processes, including platelet aggregation, vasodilation, inflammation, adipo-genesis, and bone remodeling, are regulated by the eicosanoid PGD2 [White, *et al*., 2015] . Liver-type fatty acid binding protein (L-FABP) with molecular weight (14KDa) is highly expressed in proximal renal tubular cells and hepatocytes. Injury to the proximal tubular cells causes the L-FABP gene to be upregulated, increasing both the production of L-FABP in those cells and the excretion of L-FABP through the urine. The AKI and the shift from AKI to CKD appear to be predictably linked to urinary L-FABP levels. L-FABP appears to be more accurate indicator of CKD development in T2D patients than proteinuria [Suzuki, *et al*., 2019]. The previous studied indicated the LFAPB and BTP are the emerging biomarker [S. Subapriya *et al* 2020] .The primary purpose of this study to determine the effect of glucose in BTP, and LFABP .

Study Design

It is a case control study.

Materials and Methods

In this a study (80) participants, and in this articles used (36), divided in two groups nephropathy (23) and diabetic nephropathy (13) with age (25-63 years) and BMI (19 -29 kg/m2). Investigations of this study included BTP,

L-FABP, salivary hydroxyl and amide bands, glucose ,urea and creatinine .The laboratory was used for the study's practical component chemistry and of biochemistry department in College of Medicine /University of Babylon. All of patients had been diagnosed by specialist nephrologist in Imam Sadiq Teaching Hospital / Babylon city. During the period from 1/9/2022 to 1/11/2022.

Data collection

1. **Inclusion criteria**
   - Patients with kidney impairment.
   - Age between 20-65.
   - BMI between 19-29.
2. **Exclusion Criteria**

   Liver , heart , thyroid and auto immune diseases in addition to obesity , pregnancy and smoking .

Instrumentation analysis

The random glucose, urea and creatinine by caloric spectrophotometry (CECIL CE2021), BTP and L-FABP by Elisa (biotekELx50), China kit (E4141Hu and E 2159 Hu) respectively. Salivary hydroxyl of carboxyl group and amide measured by FT-IR (Bruker) Tensor27.

Collection of (blood and saliva) samples

Blood samples (5 ml) were aspirated without the use of a tourniquet from individuals suffering from renal disease and administered with a disposable syringe. Blood is gently pushed into a gel tube and allowed to coagulate for 10–15 minutes at room temperature, and centrifuged at 3000

ppm for 10 minutes. The obtained serum was putting in Eppendorf tubes labeled with number of samples then stored at -20°C until the time of examination. While saliva was obtained from participants by putting a cotton swab into their mouths and scraping the tonsils, tongue, and inner cheek, pharyngeal swabs were used to collect saliva. The swab was then immediately placed into a sterile container, labeled with the sample number, and kept in the freezer until analysis. The swab samples measured according to the ATR-FT-IR procedure [Mahrath, *et al*., 2019] .

Statistical analysis

Statistical analysis was done by using Software package for Social Science SPSS. The normality of data distribution was tested by the "Kolmogorov-Smirnov and Shapiro-Wilk" tests. Present data were Non-normally distributed, Mann-Whitney U test was applied for comparison between two groups that expressed as a mean rank. Also spearman correlation was used to determine the presence of correlation between data variance. P value ≤0.05 consider as significant value.

Result

The study showed non-significant differences (p value > 0.05) for (age, and BMI) between patients with nephropathy and diabetic nephropathy as illustrated in Table (1) . Also the current study showed in DNP group a significantly differences (P value <0.05) of glucose ,creatinine and GFR, the mean rank (23.96 , 12.38 , 23.38) respectively and the urea did not show significant differences of studied groups as data presented in Table (2).The important result recorded was increase of BTP and LFABP in nephropathy

patients with non-significant changes when compared with DNP the mean rank (19.11 ,18.87) (17.42 ,17.85) respectively as showed in Table (3) . Also the same results are obtained for salivary hydroxyl and amide that indicated increases of these bands non significantly in NP patients, the mean rank (19.65 , 18.98) (16.46 ,17.65) respectively as in Table (4).To determine whether the changes in (BTP and LFABP) is effected by glucose or not partial correlation (BTP and LFABP) when remove the effect of blood glucose as in illustrated in Table (5) .

Table (1) Demographic data of study and control groups using Mann-Whitney U test

	Patients			Control			
Variables	Median	Minimum	Maximum	Median	Minimum	Maximum	Sig.
Age (years)	55	25	63	52	25	52	0.713
BMI (kg/m^2)	24	19	29	24	18	29	0.534

Table (2) Mean rank and sum of rank for renal function test for studied groups

Variables	Group	N	Mean rank	Sum of ranks	Sig.
Glucose	Nephropathy	23	15.41	354.50	.019
	Diabetic nephropathy	13	23.96	311.50	
Urea	Nephropathy	23	19.04	438.00	.681
	Diabetic nephropathy	13	17.54	228.00	
Creatinine	Nephropathy	23	21.96	505.00	.009
	Diabetic nephropathy	13	12.38	161.00	
GFR	Nephropathy	23	15.74	362.00	.036
	Diabetic nephropathy	13	23.38	304.00	

Table (3) Mean rank and sum of rank for BTP and LFABP for studied groups

Variables	Group	N	Mean rank	Sum of ranks	Sig.
BTP	Nephropathy	23	19.11	439.50	.645
	Diabetic nephropathy	13	17.42	226.50	
LFABP	Nephropathy	23	18.87	434.00	.779
	Diabetic nephropathy	13	17.85	232.00	

Table (4) Mean rank and sum of rank for hydroxyl and amide for studied groups

Variables	Group	N	Mean rank	Sum of ranks	Sig.
Hydroxyl	Nephropathy	23	19.65	452.00	.383
	Diabetic nephropathy	13	16.46	214.00	
Amide	Nephropathy	23	18.98	436.50	.717
	Diabetic nephropathy	13	17.65	229.50	

Table (5) Partial correlation of glucose with the BTP and LFABP in patients with kidney disease

Control Variables			LFABP	BTP
Glucose	LFABP	partial Correlation	1.000	.799
		Significance (2-tailed)	-	.000
		Df	-	32
	BTP	Correlation	.799	1.000
		Significance (2-tailed)	.000	-
		Df	32	0

Table (6) The spearman correlation between variable among the studied groups

Spearman's rho		LFABP	BTP	Hydroxyl	Amide	Glucose	Urea	Creatinine	GFR	Group
LFABP	Correlation Coefficient	1.000	.815**	-.384*	-.517**	-.052	-.056	.202	-.350*	-.078
	Sig.	.	.000	.021	.001	.762	.747	.239	.036	.650
	N	36	36	36	36	36	36	36	36	36
BTP	Correlation Coefficient	.815**	1.000	-.262	-.438**	.071	-.067	.209	-.385*	-.081
	Sig	.000	.	.122	.008	.681	.696	.222	.020	.637
	N	36	36	36	36	36	36	36	36	36
Hydroxyl	Correlation Coefficient	-.384*	-.262	1.000	.583**	-.085	-.183	-.307	.415*	-.200
	Sig.	.021	.122	.	.000	.623	.286	.069	.012	.242
	N	36	36	36	36	36	36	36	36	36
Amide	Correlation Coefficient	-.517**	-.438**	.583**	1.000	.332*	.117	-.226	.265	-.099
	Sig.	.001	.008	.000	.	.048	.497	.186	.118	.567
	N	36	36	36	36	36	36	36	36	36
Glucose	Correlation Coefficient	-.052	.071	-.085	.332*	1.000	.287	-.183	.114	.227
	Sig.	.762	.681	.623	.048	.	.090	.286	.509	.184
	N	36	36	36	36	36	36	36	36	36
Urea	Correlation Coefficient	-.056	-.067	-.183	.117	.287	1.000	.594**	-.554**	-.020
	Sig.	.747	.696	.286	.497	.090	.	.000	.000	.906
	N	36	36	36	36	36	36	36	36	36
Creatinine	Correlation Coefficient	.202	.209	-.307	-.226	-.183	.594**	1.000	-.809**	-.288
	Sig.	.239	.222	.069	.186	.286	.000	.	.000	.089
	N	36	36	36	36	36	36	36	36	36
GFR	Correlation Coefficient	-.350*	-.385*	.415*	.265	.114	-.554**	-.809**	1.000	.183
	Sig.	.036	.020	.012	.118	.509	.000	.000	.	.285
	N	36	36	36	36	36	36	36	36	36
Group	Correlation Coefficient	-.078	-.081	-.200	-.099	.227	-.020	-.288	.183	1.000
	Sig.	.650	.637	.242	.567	.184	.906	.089	.285	.
	N	36	36	36	36	36	36	36	36	36

****. Correlation is significant at the 0.05 level,**

***. Correlation is significant at the 0.01 level (2-tailed).**

Discussion

Kidney diseaseas is a functional and structural abnormalities with implications for health, and classify according to the duration [Levey,2022]. The present results indicated no significant changes of age and BMI between studied groups . This matching required to eliminate potential discrepancies in parameter findings that may occur due to the effects of these factors [Al-Aaraji, *et al*., 2019] [Al-Fartosy, 2021]. Actually DN is the main complication of diabetes mellitus, it is also the end-stage manifestation of diabetes mellitus. The pathological manifestations of DN include extracellular matrix deposition, podocyte decrease, and continuous thickening of the glomerular basement membrane. If the blood glucose cannot be controlled in time, it will accelerate the occurrence and development of DN. With the continuous improvement of people's living standards and aging, diabetes mellitus has become an epidemic disease and a problem urgently to be solved worldwide. Therefore, early clinical diagnosis and prevention are of great significance in the control of diabetes mellitus [Shi, *et al*., 2019].

BTP is a protein that belongs to the lipocalin family and has a small molecular weight. A poorer GFR was directly correlated with an increase in urine BTP concentration. BTP is a potential biomarker of renal impairment in people with diabetes. The prospective data in this paper demonstrates a relationship between BTP and the range of renal diseases.

Recently, BTP can be utilized as a biomarker of kidney damage instead of albuminuria because of its reduced molecular mass, steady production rate, ionic property, and stability. It may also identify renal disease earlier than albuminuria. [Orenes-Piñero, *et al*., 2013][Yao, *et al*., 2021]. In current study, attempt to estimate it to determine its role in detection of renal

damage DNP and to explain the effect of glucose on BTP and LFABP. In current study the BTP and LFABP increase in nephropathy more than DNP that may have referred to damage of renal regardless present of DM or not The intracellular fatty acid carrier protein known as liver-type fatty acid-binding protein (L-FABP) is mostly expressed in the liver and kidney. According to evidence, L-FABP is linked to renal tubule-interstitial injury brought on by increased free fatty acid absorption. In renal function impairment, urine L-FABP levels changed before urinary albumin levels. A stronger biomarker than ACR for the early diagnosis of DN in type 2 diabetes is the urinary L-FABP level. L-FABP, a component of fatty acid metabolism, is expressed in the proximal tubules of the human kidney.

In past clinical study, urinary excretion of L-FABP was reported to offer potential clinical marker to screen for kidney dysfunction and thereby to identify patients who are likely to experience deterioration of renal function in the future L-FABP transports free fatty acids to organelles such as the mitochondria and lysosomes for β- oxidation for use in these cellular processes[Kamijo-Ikemori, *et al*., 2011]. Actually, tubular interstitial damage was decreased by the expression of human LFABP in renal proximal tubules, Therefore , urinary LFABP will be a novel biomarker to detect the renal interstitial damage progresses [Thi, *et al*., 2020] .One of the limitation point in this study is small sample size and limited time of present study.a significant results for both parameters illustrate no effect recorded of DM and the effect mainly referred to presence of kidney damage(nephropathy). Also a partial correlation was used to exclude the effect of glucose on LFABP and BTP as in Table (5), the same result was recorded the same changes in spite of excluded the effect of glucose. that confirm present explanation.

Parameters mainly dependent on renal damage without. Also in the current study the salivary hydroxyl and amide bands decrease in diabetic nephropathy more than nephropathy .

Conclusion

The two markers (BTP and LFABP) consider as good indicator for initiation of kidney damage regardless that result from glucose or another cause.

Ethical Approval

Approval of scientific committee of Babylon Medical College (University of Babylon, Iraq) and the Biochemistry Department in the same College, Approval of scientific committee of Imam Sadiq teaching hospital and Al Hila teaching hospital/ Babylon and oral consents were obtained from all patients participating in the study according to the document number 4 in 06/07/2022 to get this approval.

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