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Original Article

Urinary C-peptide creatinine ratio is a significant indicator of non-alcoholic fatty liver disease in children with obesity

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ABSTRACT

Background. Nonalcoholic fatty liver disease (NAFLD) is the commonest etiology of chronic hepatic problems in children with obesity. This study aimed to assess whether urinary C-peptide creatinine ratio (UCPCR) might be a potential indicator of NAFLD in obese children.

Methods. The study included 240 children with simple obesity. Hepatic ultrasonic examination, anthropometric and laboratory measurements including fasting plasma glucose, fasting insulin, fasting C peptide, liver, renal profile, lipid profile, and UCPCR were obtained in all cases. According to the results of the hepatic ultrasonography, cases were classified into two categories, those with NAFLD (n=98) and without NAFLD (n= 142).

Results. In cases with NAFLD, UCPCR was significantly higher than those without NAFLD ($P < 0.001$). A significant positive correlation between UCPCR and waist circumference (WC SDS), triglyceride, fasting C-peptide, HOMA-IR and alanine aminotransferase (ALT) was found ($P < 0.001$ for each). Adjusting for other variables, UCPCR was the most significant predictor of NAFLD in children with obesity with higher odds ratio (OR = 3.26) than fasting C peptide (OR = 2.87), triglyceride (OR = 1.89), ALT (OR = 2.20), WC SDS (OR = 1.32) and age (OR=1.27) . UCPCR cut-off value of 0.755 nmol/mmol was able to discriminate cases with NAFLD from those without NAFLD with a sensitivity of 95%, a specificity of 87%.

Conclusions. We concluded that UCPCR is a useful, practical and non-invasive predictor of NAFLD in children with obesity with high sensitivity and specificity.

Key words: non-alcoholic fatty liver disease, urinary C-peptide creatinine ratio, obesity, fasting C- peptide, insulin resistance.

The commonest etiology of chronic hepatic disorders in obese children is nonalcoholic fatty liver disease (NAFLD) (36.1%).[1] It includes a range of hepatic diseases from NAFLD to nonalcoholic steatohepatitis (NASH), which may proceed to cirrhosis, hepatocellular carcinoma, as well as hepatic failure.[2] Insulin resistance is one of the characteristic features of NAFLD and is crucial in the occurrence of the disorder as associated with obese.[3] NAFLD is difficult to diagnose without diagnostic procedures because people with NAFLD are generally asymptomatic or have nonspecific symptoms.[4] Early detection of NAFLD is required, although the optimum timing, frequency, and mode of screening remain undetermined.[5] The gold standard test for the detection of NAFLD is a liver biopsy. However, it is hard to perform a liver biopsy in younger children because it is invasive and has potentially life-threatening complications.[4] Moreover, liver biopsy is subjected to, sampling errors, micro-inhomogeneity, presence of un-fragmented cores, and inter-observer variability.[6] So, in both adults and children, imaging procedures as abdominal ultrasonography are frequently used to assess the presence of fatty liver

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disease and its severity.[4] However, abdominal ultrasonography is useful in moderate to severe cases, and cannot distinguish simple steatosis from NASH.[7] A new, non-invasive, and early marker is needed for the diagnosis and prognosis of NAFLD in obese children.

C-peptide is a short-chain polypeptide that is produced with insulin in identical proportions. Because C-peptide is eliminated unchanged in the urine, it is possible to measure it in the urine.[8] Previous studies reported that 24-hour urinary C-peptide correlates well with serum C-peptide. 24-hour urine collection can be difficult and deficient urine collection is another constraint.[9,10] Evaluation of the possibility of use of C-peptide/creatinine ratio allows the use of a single-spot urine sample in a similar way as protein creatinine ratio. Up to our knowledge, no research has been done to evaluate the role of UCPCR in children with obesity and its relation to NAFLD. In this work the aim was to evaluate UCPCR in children with obesity and its relationship with NAFLD and clinical and laboratory profiles.

Material and Methods

A total of 240 obese children took part in this hospital-based cross-sectional case-control study. Obesity in children was defined as a BMI of 95th percentile or higher.[11] According to hepatic ultrasonography, obese subjects were split into two categories, obese with NAFLD (n=98) and obese without NAFLD (n=142). During the months from June 2018 to May 2019, cases were randomly selected from pediatric outpatients clinics at Assiut University Children's Hospital. Children with glucose intolerance or type 2 diabetes mellitus (HbA1C 5.7% or higher) were excluded from the study. Obese children with underlying chronic medical disorders such as genetic syndromes, secondary obesity due to endocrinopathies, familial or primary hypercholesterolemia, hereditary inborn metabolic error, or consuming medicines known to produce fatty liver were also excluded from the study. The Institutional Review Board gave their approval to the research. The parents' informed consent was obtained before the patients were enrolled.

A comprehensive medical history and examination were performed on all individuals. Anthropometric measurements included determining weight (Wt) and height (Ht) as well as body mass index (BMI). A digital weighing scale was used to measure weight in kilograms to one decimal point, and a standard stadiometer was used to measure height to one decimal place. The Egyptian Growth Reference Data were used to compute BMI using the formula: weight (kg)/height^2 (meters), as well as BMI SDS using the reference ranges.[12] Waist circumference (WC) was measured halfway between the lowest rib margin and the iliac crest and WC SDS was computed using American percentiles.[13] Tanner criteria were used to determine the pubertal stage.[14]

Laboratory investigations

The serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting glucose, fasting insulin, and fasting C-peptide were measured at 8:00–10:00 a.m. following an overnight fast of at least 12 hours. Standard enzymatic procedures and reagents (Boehringer Mannheim GmbH, Penzberg, Germany) were used to measure the levels of TC, TG, HDL-C, and LDL-C using a fully automated analyzer. The YSI 2300 STAT Plus TM Glucose & Lactate Analyzer (Ohio, USA) was used to assess fasting glucose. Insulin ELISA Kit (LDN, Nordhorn, Germany) was used to assess fasting insulin. The homeostasis model of insulin resistance (HOMA-IR) was used to determine IR using the following formula: fasting glucose (mg/dl) x fasting insulin (lU/ml)/405.[15] A cut-off level for diagnosing insulin resistance was > 2.7.[16] Fasting C-peptide was measured by human C-peptide enzyme-linked immunosorbent assay (ELISA) kit (DRG Instruments GmbH, Germany). An auto-analyzer (Abbott AXSYM system-UK) was used to determine the liver profile which

included total serum bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and albumin. The serum creatinine (Cr, mg/dl) was measured using Dimension Xp and plus chemistry analyzer using its kits; which were supplied by Siemens Technology (Illinois). A human C-peptide ELISA kit (DRG Instruments GmbH, Germany) was used to determine the level of C-peptide in the urine. Urine samples were collected in boric acid preservative 2 hours after lunch meal, following a premeal void and sent to the laboratory on the same day. On the Roche Cobas e311 platform, urinary creatinine was measured using the creatinine Jaffé reagent, and the data were utilised to calculate UCPCR (nmol/mmol).

Ultrasonography

Two radiologists who were uninformed of the study's goals and blinded to laboratory results used ultrasound to diagnose fatty liver. All ultrasonic instruments were high-end models from General Electric Company, Philips, and Mindray. Diffuse fatty liver was diagnosed in patients who met two of the following three criteria in acoustic performances[17]: (a) the liver's near-field echo is diffusely enhanced, and its echo is stronger than the kidney's; (b) the structure of the intrahepatic duct is unclear; (c) the liver's far-field echo is gradually attenuated.

Statistical analysis

The SPSS package (version 22.0), SPSS Inc., Chicago, IL, United States, was used for statistical analysis. The data were presented as a mean ± standard deviation. Pearson's analysis was performed to compute the correlation coefficients for the parameters with normal distribution, and the Student's t-test was employed to calculate the differences in means between the two groups. The correlation coefficients for the parameters with non-normal distributions were calculated using Spearman's rank correlation analysis, and the Mann-Whitney U test was used to evaluate the differences in means between the two groups. The logistic model is a suitable model for assessing if predictors are significantly linked with the response variable because the response variable is a dichotomous variable (with NAFLD or without NAFLD). As a result, logistic regression was employed to see if NAFLD is linked to any single predictor at the univariate level. The relevant factors from the univariate analysis were then used as predictors in step-wise logistic regression to find significant predictors at the multivariate level. The optimum UCPCR cutoff value for detecting NAFLD in obese children was determined using a receiver operating characteristic (ROC) curve. In all studies, a p-value of less than 0.05 was considered significant.

Results

Demographic, anthropometric, and clinical data of the study groups (Table I) shows that children with obesity and NAFLD had significantly higher BMI SDS, WC SDS, TC, TG, LDL-C, fasting insulin, fasting C-peptide, HOMA-IR, ALT and URPCR compared to children with obesity without NAFLD. The difference was statistically significant ($p < 0.05$).

Table II shows the correlation between UCPCR and clinical and laboratory variables in children with obesity and NAFLD. UCPCR was positively and significantly correlated with fasting C-peptide ($r=0.31$, $p < 0.01$), HOMA-IR ($r=0.32$, $p < 0.01$), TG ($r=0.18$, $p < 0.05$), serum ALT ($r=0.58$, $P<.001$), WC SDS ($r=0.25$, $p < 0.01$), and BMI SDS ($r=0.25$, $p < 0.01$), and inversely correlated with HDL-C ($r= - 0.32$, $p < 0.01$).

Table III shows the predictors of NAFLD and adjusted odds ratio estimated by multivariate logistic regression. Adjusting for other variables, we found that UCPCR was the most significant predictor of NAFLD in children with obesity with higher odds ratio (OR) (OR = 3.26; 95% CI: 1.467 -5.818; p = 0.000) than fasting C-peptide (OR = 2.87; 95% CI: 1.457 -3.870; p = 0.001), TG (OR = 1.89; 95% CI: 1.164- 1.251; p = 0.037), ALT

Table I. Baseline characteristics of obese children with NAFLD and without NAFLD.

Variable	NAFLD (n=98)	without NAFLD (n =142)	P value
Age (year)	11.41 ± 2.349	10.52 ± 2.52	0.001
Male/female	56/42	98/44	0.072
Obesity duration (year)	5.9 ± 3.36	5.4 ± 3.22	0.059
BMI-SDS	3.12 ± 0.60	2.23 ± 0.86	0.001
WC-SDS	3.18 ± 1.6	2. 44 ± 1.7	0.001
Puberty, n (%)			
Prepubertal	71 (72.45%)	97 (68.31%)	0.11
Pubertal	27 (27.55%)	45 (31.69%)	
Albumin (g/L)	42.35 ± 9.01	42.56 ± 7.88	0.825
Total bilirubin (mg/dl)	0.78 ± 0.29	0.64 ± 0.37	0.18
Direct bilirubin (mg/dl)	0.22 ± 0.14	0.18 ± 0.17	0.65
ALT (U/L)	39.5 ± 5.9	18 .8 ± 6.8	0.001
AST (U/L)	28.1 ± 5.7	22.5 ± 3.7	0.001
ALP (U/L)	294.27 ± 105.83	273.11 ± 87.02	0.058
GGT (U/L)	27.4 ± 8.5	18.7 ± 4.9	0.001
Serum creatinine (mg/dl)	0.66 ± 0.14	0.62 ± 0.20	0.765
TC, mg/dl	188.2 ± 45.5	156.3 ± 22.1	0.01
TG, mg/dl	153.56 ± 43.12	121.10 ± 13.56	0.01
LDL-C, mg/dl	115.5 ± 34.2	99.6 ± 11.2	0,01
HDL-C, mg/dl	44.1 ± 6.8	50.2 ± 5.8	0.02
Fasting blood glucose, mg/dl	104.3 ± 8.8	106.7 ± 9.7	0.862
Fasting insulin (mU/L)	27.2 ± 3.7	18.8 ± 4.1	0.001
Fasting C-peptide(ng/ml)	1.52 ± 0.7	1.01 ± 0.4	0.001
HOMA-IR	7.3 ± 2.7	5.0 ± 1.7	0.001
UCPCR (nmol/mmol)	0.88 ± 0.32	0.65 ± 0.23	0.001

Data are expressed as mean ± SD; ALP: alkaline phosphatase, BMI SDS: body mass index, standard deviation score, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma glutamyl transferase, TG: triglycerides, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, NAFLD: nonalcoholic fatty liver disease, HOMA-IR: insulin resistance by homoeostasis model, UCPCR: Urinary C-peptide to creatinine ratio

(OR = 2.20; 95% CI: 1.32 -2.154 ; p = 0.001), WC SDS (OR = 1.32; 95% CI 1.74- 1.581; p = 0.018) and age (OR = 1.27; 95% CI 1.21-1.54; p = 0.032) .

Receiver-operating characteristic (ROC) curves were created to determine the accuracy of UCPCR to predict NAFLD in children with obesity. UCPCR cut-off value of 0.755 nmol/mmol was able to differentiate subjects with NAFLD from those without NAFLD in children with obesity with 95% sensitivity and 87% specificity (area under the curve [AUC] 0.98; confidence interval (CI) 1.02–1.31; (p < 0.001).

Discussion

This study focused to determine the utility of UCPCR testing to identify NAFLD in a cohort of children with obesity. We observed that children with obesity with NAFLD had significantly higher UCPCR compared with those without NAFLD. Another important finding was that UCPCR is the strongest significant predictor of NAFLD in children with obesity as compared with the other factors with excellent sensitivity and specificity. To our knowledge, this is the first study to suggest that UCPCR can be utilized as a novel predictor of NAFLD in

Table II. Correlation between UCPCR and other variables in obese children with NAFLD.

Variable	NAFLD (n = 98)	
	r	P
Age (year)	0.388	0.001
Obesity duration (year)	0.067	0.566
BMI SDS	0.456	0.001
WC SDS	0.587	0.001
ALT (U/L)	0.404	0.001
AST (U/L)	0.098	0.133
GGT(U/L)	0.102	0.98
TC, mg/dl	0.112	0.021
TG, mg/dl	0.16	0.010
LDL-C, mg/dl	0.188	0.019
HDL-C, mg/dl	- 0.109	0.099
Fasting glucose, mg/dl	0.037	0.667
Fasting insulin, μU/mL	0.821	0.001
Fasting C-peptide, ng/ml	0.765	0.001
HOMA-IR	0.641	0.001

WC-SDS: waist circumference standered deviation score, BMI SDS: body mass index standered deviation score, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TG: triglycerides, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HOMA-IR: insulin resistance by homoeostasis model, UCPCR: urinary C-peptide to creatinine ratio

obese children with 95% sensitivity and 87% specificity. In accordance with the present results, another study reported that UCPCR had also high sensitivity of 97% in identifying T2DM from T1DM in children.[8] Also, another study concluded that, in non-diabetic obese children and adolescents, UCP and UCPCR are simple, fast, and reliable indicators of IR. The sensitivity of UCP and UCPCR to diagnose IR in children with obesity was 71.4% and 87.6%, respectively and the specificity was 70% and 84%, respectively.[18]

Our results were expected as the measurement of UCPCR reflects the endogenous insulin secretion which has already been established to be higher in children with obesity and NAFLD and this can discriminate it from those without NAFLD.[11,12] UCPCR is a simple, practical, non-invasive, easy test that is stable at room temperature for 3 days in a preservative which allows outpatient and home samples to be collected and sent for analysis later on.[9]

In our study, we reported that fasting C-peptide is a good predictor of detection of NAFLD in children with obesity but it is not superior to UCPCR. This was in agreement with Han et al.[19] who reported a similar result in a cross-sectional study of children with simple obesity. In line with our data, Besser et al.[10] reported that UCPCR obtained 2 hours after a home evening meal is highly correlated with 90-min stimulated C-peptide during a mixed meal tolerance test and can distinguish between maturity-onset diabetes of the young (MODY) and type 2 diabetes mellitus with a 96% sensitivity and a 97% specificity. C-peptide is a well-known indicator of B-cell secretion. Jones et al.[20] on the other hand, found that 24-hour urine C-peptide can be utilized instead of stimulated serum C-peptide measurement in the assessment of

Table III. Risk factors of NAFLD by stepwise multiple logistic regression analysis.

Variable	Beta	Standard error	Odds ratio	95% CI	p-Value
Age	0.134	0.28	1.27	1.21-1.54	0.032
WC-SDS	0.108	0.23	1.32	1.74- 1.581	0.018
TG , mg/dL	0.118	0.54	1.89	1.164- 1.251	0.037
Fasting C-peptide (ng/ml)	0.612	0.61	2.87	1.457 -3.870	0.001
HOMA-IR	0.537	0.23	1.92	1.567-1.975	0.001
ALT (U/L)	0.548	0.66	2.20	1.020 -2.154	0.001
UCPCR (nmol/mmol)	0.861	0. 13	3.26	1.467 -5.818	0.001

WC-SDS: waist circumference standard deviation score, NAFLD: non-alcoholic fatty liver disease, ALT: alanine aminotransferase, TG: triglycerides, TC: total cholesterol, HOMA-IR: insulin resistance by homoeostasis model, UCPCR: urinary C-peptide to creatinine ratio

late-onset insulin-treated diabetes. C-peptide moves through the liver without being extracted in any significant amount. As a result, the level of C-peptide is a well-known indicator of B-cell secretion. The function of fasting C-peptide in distinguishing people who have or don't have fatty liver is well recognized.[10] The assessment of serum C-peptide needs access to centrifugation followed by freezing by special laboratory techniques which are restricted only to the hospital laboratory.[19]

Our study showed a significant positive correlation between UCPCR and HOMA-IR that remains significant after regression analysis, which may indicate that UCPCR can also be a potentially useful method for the assessment of the degree of insulin resistance in NAFLD in children with obesity.[19] This is in accordance with Hassan et al.[18], who reported that in obese children, UCPCR was a better predictor of IR than UCP in a multivariate logistic regression research. This showed that UCPCR is more reliable marker for predicting IR in obese children than UCP; nonetheless, both markers have good sensitivity for predicting IR.[18]

Insulin resistance is a common feature of obesity and the link between the two has long been known, with substantial scientific and therapeutic implications.[5]

Insulin resistance may have a role in the occurrence of NAFLD in both adults and children. It is significantly linked to compensatory hyperinsulinemia in children, which inhibits free fatty acid oxidation and lipid peroxidation in mitochondria. The synthesis and buildup of harmful lipid metabolites as a result of this cascade of reactions promotes oxidative stress and hepatocellular damage.[19,21]

Up to our knowledge we reported the first work that specified a cutoff value for UCPCR and the value of 0.755 nmol/mmol at which the existence of NAFLD in obese children with obesity may be predicted with high specificity and sensitivity, at the time of diagnosis. This could lead to better management and, as a result, a better prognosis for obese children. This threshold will need to be validated in prospective trials.

It is crucial to keep in mind several limitations of this study: 1-This study was cross sectional and cannot explain the causality of various factors. Further longitudinal studies are necessary. 2- The study was conducted in a single location with a relatively small sample size. More research is needed to confirm the validity of our findings. 3- NAFLD diagnosis was based on the results of hepatic ultrasound which may have resulted in a missed diagnosis in some patients. 4- Other aspects, including lifestyle-related characteristics and nutrient consumption in the diet, should be investigated further in future studies. 5- If there is renal impairment, UCPCR test cannot be used.

This study concluded that UCPCR is a useful, practical and non-invasive predictor of NAFLD in obese children with high sensitivity and specificity.

Ethical approval

The study protocol was approved by the Ethics Committee of Faculty of Medicine, Assiut Children's University Hospital, Assiut, Egypt (33/5, may.2018). Written informed consents were obtained from the parents of all participants.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: HSF, KAM, YG; data collection: HSF, KAM; analysis and interpretation of results: YG, GMS, YF; draft manuscript preparation: KAM, YG, YF. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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