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Relationship between HbA1c level and Cardiometabolic Markers in Diabetic patients from Ngaoundere

Hémoglobine glycosylée et marqueurs de risque cardiométaboliques chez les patients diabétiques à Ngaoundéré

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RÉSUMÉ

Background. The association between HbA1c and cardiovascular disease (CVD) risk is well established. **Aim.** to investigate the association between HbA1c and selected cardiometabolic markers in diabetic patients in the Adamaoua region. **Materials and Methods.** A cross sectional study was conducted at the Hypertension and Diabetes units of the Ngaoundere Regional and Protestant Hospitals from June 2015 to February 2016 in Ngaoundere, Adamawa Region, Cameroon. Recruited participants provided a written consent and subsequently filled a questionnaire on sociodemographic data. Blood pressure (BP) and anthropometric parameters were measured. Venous blood was collected for fasting blood glucose (FBG), lipid profile, glycated hemoglobin (HbA1c) and uric acid measurements. Data were analysed using SPSS version 20.0, with statistical significance considered at $p < 0.05$. **Results.** A total of 191 diabetic participants were enrolled. The majority (78.7%) of them recorded a poor glycaemic control (HbA1c > 7.9%). HbA1c levels varied inversely with waist-to-hip ratio and directly with serum uric acid. Apart from uric acid, waist-to-hip ratio, and high density lipoprotein cholesterol (HDLc), the means of all other study variables were significantly associated with increasing HbA1c category. **Conclusion.** Glycated hemoglobin is a potential predictor of dyslipidemia, overweight, and hypertension in both diabetic and non-diabetic persons in our setting.

ABSTRACT

Contexte. Le lien entre la fraction c de l'hémoglobine glycosylée (HbA1c) et le risque cardiovasculaire est bien établi. **Objectif :** analyser la relation entre l' HbA1c et quelques marqueurs cardiométaboliques dans un groupe de sujets diabétiques de la région de l'Adamaoua. **Matériels et méthodes.** Nous avons mené une étude transversale dans les unités de prise en charge du diabète et de l'hypertension artérielle des hôpitaux Régional et Protestant de Ngaoundéré au Cameroun, de Juin 2015 à Février 2016. Après un consentement éclairé des participants, les données sociodémographiques ont été collectées ; la pression artérielle et les données anthropométriques ont été mesurées. Un échantillon de sang veineux a été prélevé chez les participants à jeun pour le dosage du glucose, des lipides, de l'HbA1c et de l'acide urique. Les données ont été analysées à l'aide du logiciel SPSS version 20.0 et les valeurs de $p < 0,05$ étaient considérées comme significatives. **Résultats :** Un total de 191 personnes diabétiques ont été recrutées. La majorité (78,7%) de ces participants avaient un mauvais controle glycémique (HbA1c > 7,9%). Il y avait une corrélation négative statistiquement significative entre le taux d'HbA1c et le rapport tour de hanche/tour de taille et une corrélation positive significative entre ce même paramètre et le taux sérique d'acide urique. A l'exception de l'acide urique, du HDLc et du rapport tour de hanche /tour de taille, tous les autres paramètres étudiés étaient significativement associés au taux HbA1c**. Conclusion :** le taux d'hémoglobine glycosylée est un potentiel facteur prédictif des dyslipidémies, du surpoids et de l'hypertension artérielle dans notre contexte, autant chez les diabétiques que les autres.

INTRODUCTION

It's well established that poor glycaemic control contribute to severe cardiovascular risk, even at foetal level [1, 2, 3-6]. HbA1c is a major marker of long-term glycaemic control. Its level is a reflection of a 2-3-month cumulative glycaemic history. Raised levels of HbA1c have been reported be associated with an increased risk of coronary heart disease (CHD) and stroke [7, 8], and correlate with severity of CHD [9]. This study set out to investigate the variation of cardiometabolic markers with HbA1c as indicator) towards identifying possible CVD risk attributable to poor glucose monitoring among known diabetic patients in Ngaoundere.

MATERIALS AND METHODS

Study design and selection criteria

This was a cross sectional study involving 191 known diabetic persons recruited at the Hypertension and Diabetes units of both the Ngaoundere Regional and Protestant Hospitals in Ngaoundere city, Cameroon from June 2015 to February 2016. Five participants were excluded post-laboratory analysis for triglyceride levels > 400 mg/dL. Denial to provide participation consent, human immune deficiency virus infection, corticosteroid therapy, pregnancy and lactation constituted exclusion criteria.

Data collection procedures

Following extensive information on the study, each participant filled a questionnaire on sociodemographic data. BP and anthropometric measurements were then taken after which fasting whole blood was collected into ethylene-diamino-tetra acetic acid (EDTA) and dry tubes for biochemical analysis.

BP measurement were obtained using a manual aneroid sphygmomanometer (ADC Prosphyg, model 770) with participants assuming a mandatory resting period of 15-20 minutes prior to measurement and upright sitting posture during measurement, in accordance with the WHO STEPs recommendation [11].

FBG levels were determined by help of a glucometer (Accu-Chek, Performa) following an 8-12 hour overnight fast in accordance with WHO recommendations [11]. As a measure of glycaemic control, FBG levels were set as <126 mg/dL, 126-140 mg/dL and >140 mg/dL respectively. HbA1 concentration was determined in EDTA whole blood samples following an ion exchange resin method [12] and the HbA1c fraction calculated as 80% of HbA1. HbA1c was classified as < 6.8%, 6.9–7.6% and > 7.6%, corresponding to good, moderate and poor glycaemic control respectively. FBG, total cholesterol, and triglyceride levels were determined following the GOD-PAP, CHOD-PAP, and TGO-PAP methods. HDLc concentrations were measured in the serum supernatants after the separation and precipitation of LDL and VLDL lipoprotein fractions mediated by a polysaccharide sulphate in the presence of divalent cations. LDLc levels were calculated following the Friedwald's formula thus: LDLc (mg/dL) = TC–TG/5–HDLc, where TC = total cholesterol and TG = triglycerides, for all corresponding triglyceride levels < 400 mg/dL [13]. Cholesterol ratio was estimated with the help of the formula TC/HDLc [14]. Serum uric acid (SUA) levels were analysed following the uricase colorimetric method, with normal values being Male: 3.6–7.0 mg/dL, Female: 2.5–6.2 mg/dL. All biochemical measurements were performed using a semi-auto biochemistry analyser (Mindray BA-88A, BH7AB2710, China) and commercially acquired kits, based on previously described methods [15,16].

Method calibration was performed using the Calimat calibrator (reference: 62321, lot number: 1003001280 Biomérieux, France) and analytical quality was ensured using the LyotrolTM N/P quality control serum (reference: 62373, lot number: 1003001280 Biomérieux, France) in conformity with Levey-Jennings and Westgard's rules. An electronic blood pressure meter (Omron HEM712C, 6416799LF, China) and a second semi-automated spectrophotometer (SECOMAM Basic/70VB0358, SN: 1790) were used to verify the reproducibility of BP and biochemical measurements at random intervals.

Data Management and Analysis

Data collected were keyed into Microsoft excel spreadsheet and controlled for concordance with the source data. The Statistical Package for Social Sciences (SPSS) version 20.0 was used for data analysis and results obtained compared with those obtained using R version 3.0.2 software. The ANOVA and Mann-Whitney U tests were used to compare means between normally and non-normally distributed data subsets respectively with statistical significances considered at $P < 0.05$.

Ethical Consideration

This study obtained ethical approval from the Ngaoundere Regional Hospital ethical committee (Ref: 2015/110/UN/DFS/CD_SBM). Prospective participants were furnished with adequate information about the study in the language best understood prior to them giving their consent to participate and subsequent enrolment. Participation was voluntary and each participant was reserved the freedom to quit the study without any related sanctions. Information obtained from participants was kept confidential, and those with abnormal results were referred to a Cardiologist.

RESULTS

Glycaemic control level of study participants

In this study, 191 known diabetic patients were enrolled with an average age of 55.30 ± 12.38 years. The majority (78.7%) of them recorded a poor glycaemic control (HbA1c > 7.9%). The distribution of participants following their HbA1c level is presented in table 1.

Table 1: Distribution of participants according to glycaemic control level

HbA1c Level	n	%
< 6.8%	29	15.18
6.9 - 7.6%	12	6.28
> 7.6%	150	78.53

HbA1c: "c" fraction of glycated haemoglobin.

Correlation between glycaemic control measures and cardiometabolic markers

The Pearson linear correlation between glycaemic control measures and selected cardiometabolic markers was studied. the corresponding outcomes are presented in table 2. Glucose levels correlated positively and significantly with cholesterol ratio, while HbA1c correlated significantly with waist-to-hip ratio and SUA.

Table 2: Correlation between FBG, HbA1c and cardiometabolic markers

Variables	FBG (Pearson)	HbA1c (Pearson)
Age	-0.076	0.047
Systolic blood pressure	-0.095	0.141
Diastolic blood pressure	-0.113	0.199
Waist Circumference	-0.083	-0.244
Hip Circumference	-0.055	-0.112
Waist-to-Hip ratio	-0.070	**-0.390****
Body Mass Index	-0.112	-0.073
Total Cholesterol	0 .069	0.157
Triglycerides	0.069	-0,023
HDLc	-0.096	0.242
LDLc	0.031	0.143
Cholesterol ratio	**0.198****	-0.047
Serum Uric Acid	-0.087	**0.300***
Fasting Blood Glucose	-	0.233

**P<0.05, **P<0.01 after correlation test. HDLc: high density lipoprotein cholesterol. LDLc: low density lipoprotein cholesterol. FBG:fasting blood glucose. HbA1c: "c" fraction of Glycated haemoglobin.*

Comparison of means of cardiometabolic markers between glucose control levels

Participants were classified according to glucose level and means of cardiometabolic markers compared between these groups (table 3). The mean total cholesterol, triglycerides, LDLc and cholesterol ratio recorded significant increase, alongside decreasing HDLc with ascending glucose categories. Furthermore, the means of anthropometric parameters and age observed significantly highest levels in patients with glucose level ranging 126-140 mg/dL. Serum uric acid levels on the contrary demonstrated a significant decrease in mean levels with increasing blood glucose.

Table 3: Comparison of means of cardiometabolic markers between glucose levels

Parameters (Mean±SD)	Fasting Blood Glucose Level			P-value
	<126 mg/dL	**126-140 mg/dL**	**>140 mg/dL**	
Age (years)	43.85±16.01	55.22±11.47	53.46±12.71	<0.001*
Systolic blood pressure (mmHg)	137.64±24.65	137.89±25.13	139.46±26.28	0.803
Diastolic blood pressure (mmHg)	89.50±14.29	90.26±13.79	91.25±15.49	0.555
Body Mass Index (kg/m^2)	24.82±5.52	27.56±4.57	26.40±7.86	0.011*
Waist Circumference (cm)	85.92±13.52	96.04±16.79	93.62±14.45	<0.001*
Hip Circumference (cm)	89.51±13.36	97.04±16.79	95.37±13.71	<0.001*
Waist-to-Hip ratio	0.96±0.05	0.99±0.06	0.98±0.09	<0.001*
Total Cholesterol (mg/dL)	217.44±54.67	238.16±53.53	246.80±89.71	0.004*
Triglyceride (mg/dL)	103.62±45.26	142.82±64.83	251.29±37.91	<0.001*
HDLc (mg/dL)	45.40±11.97	43.63±13.71	43.12±18.44	0.037*
LDLc (mg/dL)	150.23±53,19	163.12±43.19	175.22±83.87	0.039*
Cholesterol ratio	5.05±1 .63	5.73±1.42	6.35±3.15	<0.001*
Serum Uric Acid (mg/dL)	6.46±1.28	6.44±1.93	6.07±1.25	0.043*

**P<0.05 after ANOVA. SD: standard deviation. BP: blood pressure. HDLc: high density lipoprotein cholesterol. LDLc: low density lipoprotein cholesterol.*

Subsequently, HbA1c was used to categorise participants into three glycaemic control levels, and the means of study variables compared between these categories. Apart from serum uric acid, waist-to-hip ratio, and HDLc, all other study variables were significantly associated with HbA1c levels. With the exception of BMI which recorded highest significant mean values in patients with HbA1c levels ranges from 6.9% to 7.6%, the means of other anthropometric measures, age, BP and lipid profile parameters recorded highest significant concentrations in patients categorised with HbA1c > 7.6% (Table 4).

Table 4: Comparison of means of cardiometabolic markers between glycaemic control levels

Parameters (Mean ± SD)	HbA1c levels			P-value
	< 6.8%	**6.9–7.6%**	**> 7.6%**	
Age (years)	38.05±13.73	34.56±13.72	54.85±11.35	<0.001*
Systolic blood pressure (mmHg)	133.42±21.37	133.78±18.14	143.90±25.29	0.023*
Diastolic blood pressure (mmHg)	87.69±12.01	92.67±10.19	96.07±14.92	0.001*
Body Mass Index (kg/m^2)	23.80±4.74	27.35±7.22	26.12±6.08	0.035*
Waist Circumference (cm)	82.02±11.36	81.44±13.98	92.95±13.49	<0.001*
Hip Circumference (cm)	85.84±11.15	85.44±13.64	95.39±13.79	<0.001*
Waist-to-Hip ratio	0.96±0.05	0.95±0.03	0.98±0.04	0.076
Total Cholesterol (mg/dL)	214.62±56.66	214.67±69.13	258.11±101.66	0.008*
Triglyceride (mg/dL)	95.66±40.55	94.54±39.88	115.93±44.75	0.018*
HDLc (mg/dL)	46.40±11.80	42.55±7.00	45.91±14.33	0.512
LDLc (mg/dL)	147.87±53.87	153.19±60.82	185.57±96.56	0.009*
Cholesterol ratio	4.87±1.65	5 .09±1.56	5.81±2.00	0.017*
Serum Uric Acid (mg/dL)	6.38±1.15	6.03±0.61	6.46±0.91	0.596

**P<0.05 after ANOVA. SD: standard deviation .BP: blood pressure. HDLc: high density lipoprotein cholesterol. LDLc: low density lipoprotein cholesterol. HbA1c: "c" fraction of Glycated haemoglobin.*

DISCUSSION

Generally, diabetic persons run high risk of several complications especially in conditions of poor glycaemic control, thus the principal objective of glucose lowering and long-term glycaemic control in diabetes management. In the present study, 78.53% of diabetic participants had a poor level of diabetic control (HbA1c > 7.6%). This huge proportion could be the effect of poor diabetes management attributable to either patient and/or health system/healthcare factors. In a previous study involving diabetic participants aged 10 to 20 years, the authors recorded 61% of type 1 and 45% of type 2 diabetic participants (59% of total participants) with HbA1c > 7.9% [17].

In this study, blood glucose levels correlated with cholesterol ratio, while HbA1c levels varied directly with SUA and inversely with waist-to-hip ratio. A Nepalese study in 2011 reported significant positive correlations between HbA1c and total cholesterol, LDLc, LDLc/HDLc ratio, Non-HDLc and Risk ratio in diabetic patients [18], in line with the findings of Petitti et al [17]. and Kim et al [19]. Khan and co-workers reported that both HbA1c and FBG demonstrated significant correlations with cholesterol, TG and LDLc and inverse variations with HDLc [20]. Surprisingly, FBG and HbA1c failed to demonstrate a significant correlation, of which some authors have previously reported a direct variation between them [18]. The disparities observed between our study population and the previous studies can be attributed to the differences in pharmacotherapy among our patients, including well established conventional drugs and poorly studied indigenous (traditional) medicines. Also, the possible existence of inconsistencies in medical visits/follow-up and non-adherence to pharmacotherapy, recommended diet and lifestyle modification among our patients could be a potent source of irregularities in the current study.

Following the categorisation of diabetic participants based on HbA1c levels, and with the exception of waist-to-hip ratio, HDLc and SUA, the mean levels of all other studied cardiometabolic markers were observed to be significantly high in the "moderate" and "poor" glycaemic control categories. Likewise, the means of study variables were observed to significantly increase with ascending blood glucose category but for blood pressure parameters, while

the mean HDLc levels decreased significantly. Again our findings corroborated with those of Vinod Mahato et al where diabetic persons with HbA1c levels > 7.0% portrayed significant increases in the mean TC, LDLc, TG, LDLc/HDLc ratio, Non-HDL-C and Risk ratio (TC/HDLc) without any significant alteration in mean HDLc compared to patients with HbA1c value ≤ 7.0%[18]. In the same direction, another study reported significant alterations in lipid parameters (with the exception of LDLc) between three different glycemic control groups of diabetic patients thus: good (HbA1c<6%), poor (HbA1c > 6%–9%) and worse (HbA1c > 9%)[20]. Also, in the SEARCH study among young diabetic persons, poorer glycemic control was neither associated with HDLc concentration in type 1 nor type 2 diabetes [17]. Conversely, Laverdy and colleagues reported higher mean triglycerides and HDL levels in type 2 diabetic participants having HbA1c > 6.5% compared to those with HbA1c ≤ 6.5%: total cholesterol and HDL demonstrated non-significant differences [21].

Several studies have highlighted HbA1c to be not only a marker for glycaemic control, but also a predictor of dyslipidaemia [18, 20]. The present study likewise demonstrated alterations in cardiometabolic markers with ascending levels of both FBG and HbA1c among a diabetic patients as well as the non-diabetic controls. In areas characterised with resource deficiency, accessibility to the usually scarce healthcare services represents a major pitfall in diabetes management, coupled with the inadequacies in personnel and infrastructural capacity, alongside sociocultural and anthropological barriers.

CONCLUSION

The present study portrayed evidence of valuable associations between glycaemic control and cardiometabolic parameters in both diabetic and non-diabetic individuals. More adaptive methods are required to curb the occurrence of dyslipidaemias, CVDs and other diabetes complications, and slow down their progression in our context.

FURTHER RESEARCH AND PERSPECTIVES

Several studies reiterate the role of poor glycaemic control in increasing the occurrence of dyslipidaemias. More rigorous study designs are envisaged to determine the periodic clinical and biochemical variations with glycaemic control level, establish cause-and-effect relationship, and evaluate patients' adherence to recommended therapy, while investigating pertinent specific determinants of poor glycaemic control thereof at both personal and population levels.

AUTHORSHIP CONTRIBUTIONS

Conception and design: OPM, TJON. Acquisition of data: MTT, AMT, HSH and PDA. Analysis and interpretation of data: MTT, AMT, HSH. Drafting the article: MTT and PDA. Revising the article: OPM, MTT, TJON, and AJM. Final approval of the version: OPM, TJON, AJM and MTT

CONFLICTS OF INTEREST

The authors declare that there are no conflict of interest regarding the publication of this work.

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