

## ACUTE PHASE REACTANT PROTEINS, ANTHROPOMETRIC AND DYSLIPIDAEMIC CHANGES ASSOCIATED WITH TYPE 2 DIABETIC MELLITUS AMONG NIGERIAN POPULATION

\*Ekun, O. A., Sangotokun, O. A., Eweje, O. A., Azenabor, A. and Akinloye, O.

Department of Medical Laboratory Science, College of Medicine of the University of Lagos.

\*Author for Correspondence. E-mail: ayodele1619.oe@gmail.com; Tel: +2348033151619

(Received: 23<sup>th</sup> June, 2018; Accepted: 22<sup>nd</sup> September, 2018)

### ABSTRACT

Diabetes mellitus is a serious metabolic disorder of multiple aetiology. This disorder is on the increase in some developing countries such as Nigeria. It is characterized by chronic hyperglycaemia with disturbances in carbohydrate, fat and protein metabolism resulting from either defects in insulin secretion, insulin action or both. In some cases, the disease may be insidious until the patients develop complications. A total number of three hundred and seventy five individuals participated in this study out of which two hundred and twenty five were type 2 diabetic mellitus volunteers while one hundred and fifty served as control. Anthropometric measurements were taken using weighing balance, tape rule, and meter rule. C-reactive protein, fasting blood glucose, total protein, albumin and lipid profile were determined using enzyme-linked immunosorbent assay (ELISA) and Cobas chemistry auto analyzer respectively. There were a significant increase ( $p < 0.05$ ) in weight, body mass index (BMI) waist hip ratio, fasting blood sugar, C-reactive protein, total cholesterol, triglyceride, triglyceride/high density lipoprotein (TG/HDL), low density lipoprotein/ high density lipoprotein (LDL/HDL) and TC/HDL in type 2 diabetic mellitus patients when compared with the controls. On the other hand, albumin, albumin globulin ratio and HDL were observed to be significantly ( $p < 0.05$ ) low in diabetic volunteers when compared with controls. There was a positive association ( $r = 0.66, p < 0.05$ ) between C-reactive protein (CRP) and glucose whereas a negative association ( $r = -0.31, p < 0.05$ ) was observed between CRP and albumin among diabetic mellitus group. This study suggests that diabetes mellitus is associated with increased risk of inflammation and lipid dysfunction.

**Key words:** Diabetes mellitus, Acute phase reactants, Lipid profile, Blood sugar.

### INTRODUCTION

Diabetes mellitus (DM) is one of the non-communicable diseases of multiple aetiology. It is a disorder that is usually characterized by chronic hyperglycaemia as well as disturbances of carbohydrate, fat and protein metabolism (WHO, 1999, WHO, 2016). It is a consequence of defects in insulin secretion, insulin action, or both (WHO, 1999; WHO, 2016). Type 2 diabetes mellitus (T2DM) on the other hand is seen in individuals who have insulin resistance. This resistance is usually as a result of relative insulin deficiency (Sato *et al.*, 2009). The World Health Organization report (2016) indicated that about 422 million people are diabetic world-wide as at 2014. It has been reported that type 2 diabetes mellitus account for the majority (about 90% ) of the diabetes mellitus cases (Tripathi and Srivastava, 2006; Mbanya, 2007; CDC, 2011; Shi and Hu, 2014).

Adult with diabetes mellitus have been shown to have two to four fold increased risk of

cardiovascular events (Fox *et al.*, 2004). Thus cardiovascular complications have been shown to account for about 80% of premature excess mortality in individuals with diabetes mellitus (Winer and Sowers, 2004). Moreover, it has been shown that diabetes mellitus is associated with vascular complications; this is usually caused by micro-and macro angiopathy. Thus retinal and renal micro-angiopathies cause diabetic retinopathy and nephropathy respectively. Accelerated forms of atherosclerosis accounts for macro-angiopathy in diabetes mellitus. This usually affects the coronary, carotid and peripheral arteries leading to increased risk of myocardial infarction, stroke and diabetes foot disease (Duby *et al.*, 2004)

On the other hand, acute-phase proteins are a class of proteins whose plasma concentrations increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation (Cray *et al.*, 2009). It has been shown that positive acute-phase proteins

usually increase in concentration in diabetes mellitus (Herpers *et al.*, 2009).

Previous studies have suggested a possible link between subclinical chronic inflammation and the pathogenesis of type 2 diabetes mellitus (Pickup *et al.*, 1997; Pickup and Cook, 1998). Inflammation is a short-term adaptive response of the body as a component of tissue repair to deal with injuries and infections (Badawi *et al.*, 2010). It has been suggested that in obese individual, there is an abnormal level of fatty acids that enhance chemokine release by the expanding adipose tissue (Badawi *et al.*, 2010). This leads to activation of monocytes as well as increased secretion of pro-inflammatory adipokines, which in turn leads to insulin resistance in adipose tissue and other tissues, thus increasing the risk of type 2 diabetes mellitus (Larsen and Henson 1983, King, 2008). A study has also suggested that inflammatory responses possibly elicit dual roles in type 2 diabetes mellitus; it may have either a causal relationship leading to resistance to insulin or may be intensified by hyperglycaemic state resulting in type 2 diabetes mellitus complications (Nathália *et al.*, 2013). Thus it has been estimated that about 25% of new onset of Type 2 diabetes mellitus is associated with evidence of systemic inflammation at the time of diagnosis (Zhang *et al.*, 2009). There is a need to investigate some inflammatory markers as well as lipid among type 2 diabetic Nigerians as it is obvious that diabetes mellitus is gradually becoming a pandemic medical condition among Nigerian population. Thus this study intends to evaluate some acute phase reactant proteins and lipid among Nigerian volunteers with diabetes mellitus.

## MATERIALS AND METHODS

### Study Design

This was a cross sectional study conducted among diabetic patients that exhibited good glycaemic control at Lagos University Teaching Hospital. The patients were chosen irrespective of their mode of treatment. Informed consent was taken from the patients. A total of three hundred and seventy five (375) volunteers consisting of two hundred and twenty five (225) diabetic volunteers and one hundred and fifty (150) non-diabetic volunteers as control.

### Inclusion and Exclusion criteria:

**Inclusion:** Adult male and female diabetic mellitus individual not less than 40 years of age (however recent 2016 WHO report on diabetes has indicated that type 2 diabetes can be seen in children) and had a good glycaemic control were all included. The cut off glucose value used for inclusion of diabetes mellitus was fasting blood glucose of  $\geq 126$  mg/dl (7.0 mmol/l) (WHO, 2006) and fasting blood glucose of  $\leq 100$  mg/dl (5.56 mmol/l) (ADA, 2003) for non-diabetic individuals (as control).

### Exclusion Criteria:

Diabetic patients with clinical evidence of diabetic complications of renal disease, retinopathy, neuropathy and liver disease were excluded from the study.

### Ethical Consideration

Approval was obtained from the Research and Ethics Committee (ADM/DCST/HREC/122 and ADM/DCST/HREC/2175) of the Lagos University Teaching Hospital (LUTH) prior to the commencement of the study.

Informed consent was sought from each of the participants of the study prior to participating in any of the procedures of the study.

### Data Analysis

The data collected from the study were analysed using SPSS version 21.0. Descriptive statistics of mean, standard deviation, t-test, Pearson correlation and bar chart were used to present the data. The level of significance was set at  $p < 0.05$ .

### Methods:

Blood glucose, total protein, albumin total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL) and low density lipoprotein (LDL) were analyzed using Cobas C111 chemistry auto analyzer.

### hs-CRP

Serum CRP (hs-CRP) estimation was carried out using Enzyme-Linked Immunosorbent Assay (ELISA) based on the method of Engvall, and Perlmann, (1971), Engvall, and Perlmann, (1972).

## RESULTS AND DISCUSSION

In this study, anthropometric measurements of body mass index, waist circumference and waist-hip ratio were evaluated (Table 1). We observed a significant increase ( $p < 0.05$ ) in waist-hip ratio of the diabetic volunteers when compared with the non-diabetic group. There was no significant difference ( $p > 0.05$ ) in the mean age, body mass index and waist circumference in the two groups studied. A significant increase in waist-hip ratio a measure of central obesity among diabetic volunteers is probably an indication of central obesity among diabetes mellitus group. Previous

study has shown an association between increase in waist-hip ratio and diabetes mellitus (Schmidt *et al.*, 1992), thus suggesting that central obesity may be independently associated with type 2 diabetes mellitus. Another study on waist-hip ratio among type 2 diabetes mellitus suggested that an increase in waist-hip ratio is positively associated with complications among this group of individuals (Stuhldreher *et al.*, 1994). A recent study has also suggested that there is a genetic association between waist-to-hip ratio and type 2 diabetes mellitus as well as chronic heart disease (Emdin *et al.*, 2017).

**Table 1.** Anthropometric Characteristics of the Volunteers.

	<b>Diabetic Mean <math>\pm</math> S.E.M n=225</b>	<b>Non- Diabetic Mean <math>\pm</math> S.E.M n=150</b>	<b>p-value</b>
Age (years)	55.22 $\pm$ 8.12	56.59 $\pm$ 9.35	0.13
BMI (kg/m <sup>2</sup> )	25.67 $\pm$ 3.66	25.71 $\pm$ 3.94	0.94
Waist circumference (cm)	87.97 $\pm$ 10.42	87.42 $\pm$ 10.86	0.81
Waist/hip (ratio)	0.94 $\pm$ 0.08	0.91 $\pm$ 0.09	0.04*
Systolic blood pressure (mmHg)	137.93 $\pm$ 18.97	134.85 $\pm$ 18.97	0.64
Diastolic blood pressure (mmHg)	86.14 $\pm$ 10.58	85.25 $\pm$ 9.73	0.53

\*significant p value ( $p < 0.05$ )

Furthermore, in table 1, it was observed that there was no significant difference ( $p > 0.05$ ) in the systolic and diastolic blood pressure of the two volunteered groups studied. This observation might have suggested that the diabetic group selected for this study did not manifest hypertension co-morbidity as at the time of this study. Previous studies have demonstrated that tight blood glucose and blood pressure control decreased the risk of any diabetes related endpoint by 12% and 24% respectively (UK Prospective Diabetes Study group 33, 1998; UK Prospective Diabetes Study group 38, 1998). It has been demonstrated also that a tight control of blood

pressure among type 2 diabetes mellitus reduces the risk of death related to diabetes mellitus by 32% (UK Prospective Diabetes Study group 38, 1998).

Moreover in table 2, we observed a significant increase ( $p < 0.05$ ) in the plasma glucose concentration of type 2 diabetes mellitus group when compared with the non-diabetes control group. This is an expected observation based on the group of volunteers studied. One of the common finding with diabetes been a metabolic disorder is that it is characterized by hyperglycaemia (WHO, 2016).

**Table 2:** Comparative analysis of Glucose, C-reactive protein (CRP), Albumin, Total protein, Globulin and Albumin/Globulin ratio in Diabetics and Non-Diabetics

Variables	Diabetic	Non-Diabetic	t-value	p-value
	Mean $\pm$ S.E.M n = 225	Mean $\pm$ S.E.M n = 150		
Plasma Glucose (mg/dl)	162.64 $\pm$ 3.21	72.73 $\pm$ 1.29	26.01	0.000*
hs-CRP (mg/l)	4.09 $\pm$ 0.91	1.30 $\pm$ 0.50	2.69	.009*
Total protein (g/l)	73.50 $\pm$ 1.85	77.64 $\pm$ 0.71	0.43	.0664
Albumin (g/l)	43.48 $\pm$ 0.76	46.99 $\pm$ 1.28	2.36	0.02*
Globulin (g/l)	30.02 $\pm$ 1.62	30.65 $\pm$ 0.78	-1.22	0.229
Albumin/globulin ratio	1.45 $\pm$ 0.16	1.53 $\pm$ 0.06	3.05	0.004*

\*Significant level:  $p < 0.05$

There was a significant increase ( $p < 0.05$ ) in the mean value of hs-CRP among diabetic group (Table 2). This observation agrees with the previous studies of Ford (1999), Festa *et al.* (2000), and Frohlich *et al.* (2000) where it was observed that interleukin 6 (IL-6) and C-reactive protein, the two sensitive physiological markers of subclinical systemic inflammation, are associated with hyperglycaemia, insulin resistance, and overt type 2 diabetes mellitus (DM). Thus from this study, it became evident that the diabetic group might have been undergoing some inflammatory processes which in the long run could predispose them to either microvascular or macro-vascular complications. It has been suggested that the link between diabetes and inflammation is a reciprocal process (de Rekeneire *et al.*, 2006). This is because inflammation may contribute to diabetes onset while diabetes on the other hand may contribute to continued inflammation (de Rekeneire *et al.*, 2006). Study has shown that hyperglycaemia mediate formation of advanced glycosylation end-products. These end-products have been suggested to contribute to inflammation by producing a chronic stimulation for secretion of cytokines (Brownlee, 1995). Apart from this, some studies have associated increase in CRP with future cardiovascular complications among type 2 DM (Lindberg *et al.*, 1991, Ridker *et al.*, 1997). Cardiovascular events on the other hand have been noted to be important cause of diabetes mellitus deaths accounting for 15% of all DM deaths in Nigerians (Ogbera *et al.*, 2009).

Furthermore we observed a non-significant decrease ( $P > 0.05$ ) in the total protein value of the diabetic when compared with the control group. However serum albumin and albumin globulin ratio were significantly lower in the diabetic group ( $p < 0.05$ ). Our finding with respect to albumin is in consonance with the previous study of Shaper *et al.*, (2004) where a significant lower result was observed in albumin among type II DM. This might suggest that albumin is a negative acute-phase reactant protein (Ritche *et al.*, 1999), as it has been shown that negative acute-phase proteins are reduced in response to inflammation (Herpers *et al.*, 2009).

In addition to this, the degree of association between glucose, acute phase reactant proteins and marker of inflammation were evaluated (Table 3). We observed a positive and significant ( $p < 0.05$ ) association between glucose and CRP. This observation suggests that hyperglycaemia could provide a template for inflammatory processes as increase in CRP clearly suggests inflammatory activities. It has been suggested that inflammation plays a pivotal role in the pathogenesis of type 2 diabetes mellitus and its complications (Donath and Shoelson, 2011). Studies have shown that dysglycaemia is associated with inflammation in diabetic individuals as well as individuals with impaired fasting and impaired glucose tolerance results (Barzilay *et al.*, 2001, de Rekeneire *et al.*, 2006). Thus it has been shown that type 2 diabetes mellitus is associated with higher levels of CRP,

interleukin-6 and tumour necrosis factor- $\alpha$  markers of subclinical systemic inflammation (Yudkin *et al.*, 1999, Barzilay *et al.*, 2001). A low-grade systemic inflammation has been seen to play an important role in the pathogenesis of some glucose disorder in adults (Pickup and Crook,

1998). It has been suggested that visceral fat contribute the most to the attenuation of the association between diabetes and inflammation. This could possibly explain the relationship between diabetes and C-reactive protein as also observed in this study.

**Table 3.** Ratio of Lipid Profile between Diabetic participants and Non-Diabetic participants

	<b>Diabetic</b>	<b>Non-diabetic</b>	<b>P value</b>
	<b>Mean <math>\pm</math> SD</b>	<b>Mean <math>\pm</math> SD</b>	
	<b>n = 225</b>	<b>n = 150</b>	
TC/HDL ratio	6.3 $\pm$ 2.45	3.30 $\pm$ 0.65	0.05*
TG/HDL ratio	6.6 $\pm$ 1.87	3.61 $\pm$ 0.81	0.04*
LDL/HDL ratio	4.0 $\pm$ 1.96	1.75 $\pm$ 0.44	0.03*

\*significant p value ( $p < 0.05$ )

Thus adiposity in particular visceral adipose tissue, has been found to be an important promoter of low-grade chronic inflammation (Forouhi *et al.*, 2001, Pannacciulli *et al.*, 2001). It is important to know that a negative and significant relationship ( $p < 0.05$ ) existed between CRP and albumin. This observation possibly confirms the fact that CRP is a positive acute phase reactant, while albumin on the other hand is a negative acute phase reactant.

Figure 1 and table 3 show comparative analysis of serum lipid and lipid ratio respectively. Significant increase ( $p < 0.05$ ) in the levels of total cholesterol, LDL-cholesterol and triglyceride, as well as a significant decrease ( $p < 0.05$ ) in HDL-cholesterol were observed in the diabetic mellitus volunteers. Our finding with respect to lipid profile suggests that type 2 diabetes mellitus may be associated

with dyslipidemia. Thus our findings are in consonance with the previous study of Nakhjavani *et al.*, (2006) who observed that there was an alteration in the lipid profile in diabetes mellitus. Dyslipidemia according to Barret-connor *et al.*, (1982) was observed to predispose diabetic mellitus patients to cardiovascular complications with time. It has been suggested that in type 2 diabetes mellitus, insulin resistance increases mobilization of free fatty acid from adipose tissue. There is increased hepatic production of very low density lipoprotein via lipogenesis as well as decreased apolipoproteins B degradation, resulting in low HDL-cholesterol, high triglycerides (TGs), Increased apolipoproteins B synthesis and small dense LDL-particles (Cannon, 2008).

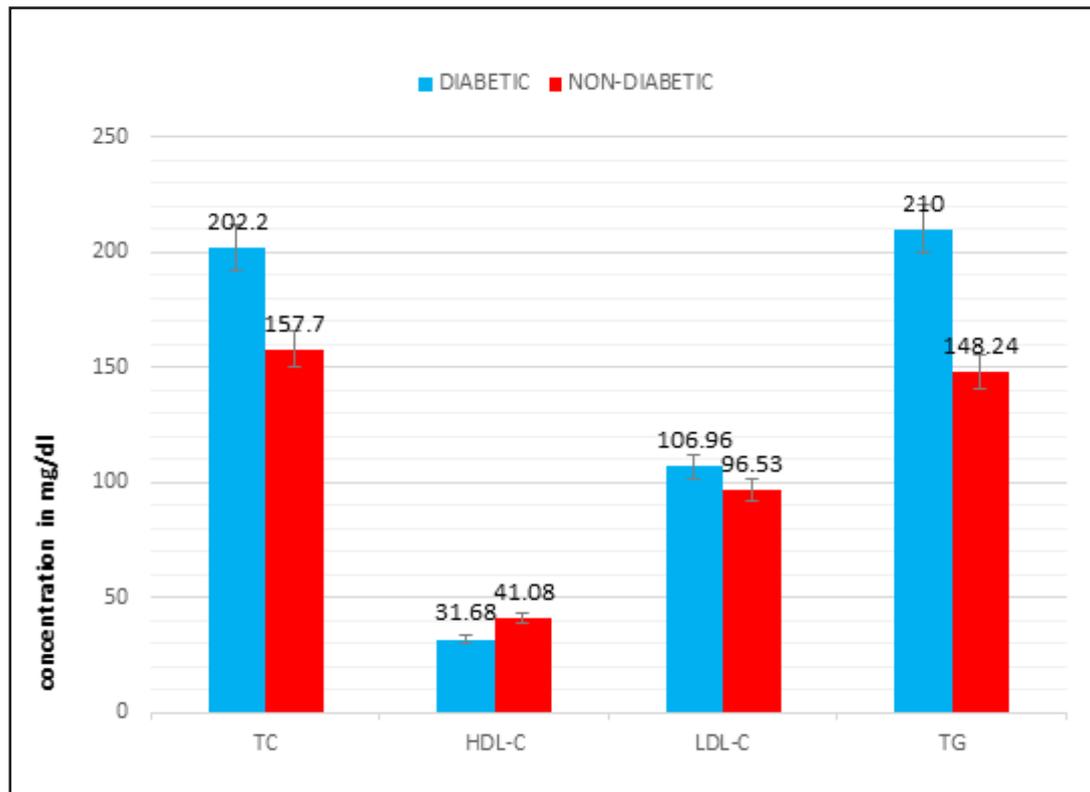


Figure 1: Showing Concentration of Lipid Analytes in Diabetic and Non-diabetic Participants

Table 4: Pearsons' Correlation between parameters in Diabetic subjects

Association between variables	Correlation coefficient (r)	p value
Glucose vs CRP	0.66	0.000*
CRP vs Total protein	0.04	0.626
Total protein vs Glucose	0.03	0.865
Albumin vs Glucose	-0.11	0.455
Globulin vs Albumin	-0.17	0.278
CRP vs Albumin	-0.31	0.035*
Total protein vs Albumin	0.53	0.000*

\*Significant level:  $p < 0.05$  CRP = C-reactive protein.

Thus it has been shown that the dense LDL-particle subtype is more inclined to oxidation, playing an important role in atherogenesis. Thus in type 2 diabetes mellitus, atherogenic dyslipidemia (as characterized by low HDL-cholesterol and apo A, elevated fasting or 2 hour post prandial triglyceride, elevated LDL-cholesterol and apo B) is a predictor of cardiovascular risk (Sorrentino *et al.*, 2010). It is interesting to note that high density lipoprotein cholesterol (HDL-C) acts by enhancing the removal of cholesterol from the peripheral tissues

and so reduces the body's cholesterol pool. However in this study we observed a significantly low HDL-C ( $p < 0.05$ ) among the diabetic group. This observation with respect to low HDL-C observed in diabetic group might have possibly compromised the effective removal of cholesterol from the peripheral tissues of this group of individuals thus leading to increased body cholesterol pool. It has been shown that in type 2 diabetes mellitus, the protective function of HDL-cholesterol may be lost due to alteration of protein resulting in a pro-oxidant inflammatory

phenotype (Sorrentino *et al.*, 2010).

Previous study has shown that low HDL-cholesterol concentrations are often accompanied by high triglycerides levels (Assman and Schulte, 1993). As observed in this study, there was a significantly low HDL-C and a significantly raised triglyceride among diabetic volunteers that participated in this study. This combination has been strongly associated with an increased risk of Coronary Heart Disease (Assman and Schulte 1993; Chapman *et al.*, 2011; Miller *et al.*, 2011). Other studies have shown that a low HDL-cholesterol in the presence of a normal LDL-cholesterol is an independent cardiovascular risk marker (Barter *et al.*, 2007, Baigent *et al.*, 2010).

A significantly ( $p < 0.05$ ) raised TG/HDL, LDL/HDL and a borderline TC/HDL ratio among the diabetic mellitus group (Table 3) were observed. These findings agree with the previous findings of Grundy (2006) where he described the dyslipidemic state as lipid triad and their associated atherogenic effect. It has been shown that lipid ratios are good predictors of cardiovascular events (Di Angelantonio *et al.*, 2009). Previous studies have shown that the diagnosis of diabetes doubles the cardiovascular risk in men and more than triples the risk in women (Haffner *et al.*, 1998; Mogensen, 2003). Thus the lipid ratios evaluated in this study gives a clearer and direct risk index of diabetic mellitus group to cardiovascular complications. As previous study has shown that the higher the lipid ratios the higher the risk index of cardiovascular complications among the diabetic mellitus subjects (UKPDS 1995).

Furthermore, table 4 showed the level of association between some analytes measured. There was an inverse relationship between CRP and albumin ( $p < 0.05$ ). Albumin and glucose on the other hand showed a non-significant inverse relationship ( $p > 0.05$ ). There was a positive association between CRP and glucose as well as between total protein and albumin. A positive correlation between glucose and C-reactive protein possibly suggests that hyperglycemia is associated with inflammation (Ford, 1999; de Rekeneire *et al.*, (2006). It has been suggested that a low grade inflammation contributes to the

pathogenesis of diabetes mellitus (Pickup and Cook, 1998). Also, previous report has suggested that elevated C-reactive protein and tumor necrotic factor- $\alpha$  are associated with worse cardiovascular outcomes (Kablak-Ziembicka *et al.*, 2011). Thus it appears that hyperglycemia (as often seen in diabetes mellitus) with elevated C-reactive protein (marker of inflammation) may possibly predispose diabetes mellitus individuals to cardiovascular complications. An inverse but insignificant relationship existed between albumin and glucose. It has been shown that poorly controlled diabetes mellitus is associated with lower plasma albumin concentration (Rodriguez-Segade *et al.*, 2005). This might possibly explain the reason for this observation. However, it has been shown that albumin plays a cardio-protective role (Daneh *et al.*, 1998, Djousse *et al.*, 2002). Thus lower serum albumin concentrations were associated with increased risk of coronary heart disease, cardiovascular mortality and carotid atherosclerosis (Daneh *et al.*, 1998, Djousse *et al.*, 2002). Hence a positive correlation between hyperglycemia and CRP as well as lower albumin concentrations in diabetes mellitus volunteers are worthy of note.

## CONCLUSION

From this study it could be concluded that diabetes mellitus is associated with dyslipidemia, increased C-reactive protein, decreased albumin and albumin/globulin ratio.

**Acknowledgment:** Authors are grateful to clinicians and nurses that assisted in recruiting the volunteers for this study.

**Conflict of interest:** None declared.

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