Case Control Study

Exercise-induced albuminuria *vs* circadian variations in blood pressure in type 1 diabetes

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Data sharing statement: Data are available from the corresponding author upon request at sobngwieugene@yahoo.fr.

Abstract

AIM

To investigated the relationship between exercise-induced ambulatory blood pressure measurement (ABPM) abnormalities in type 1 diabetes mellitus (T1DM) adolescents.

METHODS

We conducted a case-control at the National Obesity Center of the Yaoundé Central Hospital, Cameroon. We compared 24 h ABPM and urinary albumin-to-creatinine ratio (ACR) at rest and after a standardized treadmill exercise between 20 Cameroonian T1DM patients and 20 matched controls. T1DM adolescents were aged 12-18 years, with diabetes for at least one year, without proteinuria, with normal office blood pressure (BP) and renal function according to the general reference

population. Non-diabetic controls were adolescents of general population matched for sex, age and BMI.

RESULTS
Mean duration of diabetes was 4.2 ± 2.8 years. The mean 24 h systolic blood pressure (SBP) and diastolic blood pressure (DBP) were respectively 116 ± 9 mmHg in the diabetic group *vs* 111 ± 8 mmHg in the non-diabetic (*P* = 0.06), and 69 ± 7 mm Hg *vs* 66 ± 5 mm Hg (*P* = 0.19). There was no difference in the diurnal pattern of BP in diabetes patients and non-diabetic controls (SBP: 118 ± 10 mmHg *vs* 114 ± 10 mmHg, *P* = 0.11; DBP: 71 ± 7 mmHg *vs* 68 ± 6 mmHg, *P* = 0.22). Nighttime BP was higher in the diabetic group with respect to SBP (112 ± 11 mmHg *vs* 106 ± 7 mmHg, *P* = 0.06) and to the mean arterial pressure (MAP) (89 ± 9 mmHg *vs* 81 ± 6 mmHg, *P* = 0.06). ACR at rest was similar in both groups (5.5 mg/g *vs* 5.5 mg/g, *P* = 0.74), but significantly higher in diabetes patients after exercise (10.5 mg/g *vs* 5.5 mg/g, *P* = 0.03). SBP was higher in patients having exercise-induced albuminuria (116 ± 10 mmHg *vs* 108 ± 10 mmHg, *P* = 0.09).

CONCLUSION
Exercise-induced albuminuria could be useful for early diagnosis of kidney damage in adolescents with T1DM.

Key words: Albuminuria; Blood pressure; Ambulatory blood pressure measurement; Exercise; Type 1 diabetes

Core tip: Diabetic nephropathy (DN) is a major complication of type 1 diabetes mellitus (T1DM). Therefore, strategies for early detection are of critical importance. Ambulatory blood pressure measurement is useful for detection of precocious abnormalities in the occurrence of DN and exercise-induced albuminuria has been proposed as a potential predictor of DN. Our study therefore aimed to investigate the relationship between exercise-induced albuminuria and ambulatory blood pressure measurement abnormalities in T1DM Cameroonian adolescents. We found that T1DM patients had higher nocturnal and 24 h blood pressure figures than non-diabetics suggesting that exercise-induced albuminuria could be useful early detection of diabetes kidney injuries in T1DM.

INTRODUCTION
Diabetes nephropathy is the major life-threatening complication of type 1 diabetes mellitus (T1DM)[1,2].

Abnormal albumin excretion has been shown to predict the development of clinically significant nephropathy in T1DM. Indeed, persistent minimal elevation of albuminuria at rest predicts the development of more severe proteinuria and clinical diabetic nephropathy, which frequently progresses to renal failure[3]. In T1DM, nephropathy develops in 30% to 40% of cases and impaired renal function or end-stage kidney disease affect up to a third of patients[4]. Thus, strategies for early detection and for preventative interventions are of critical importance since interventions at these late stages of disease may only slow but not completely arrest the inexorable progression towards renal failure[5,6]. In this direction, it has been shown that physical exercise can stimulate albuminuria in diabetes patients and can be a useful provocative test to detect early renal abnormalities[7]. However, there is still limited evidence on its value for early detection of renal disease in T1DM.

Previous studies has proven that during exercise, urinary albumin excretion rate is more increased in long term T1DM patients thus, at risk of developing diabetes nephropathy than in general population[8]. In the contrary, some evidence suggest that the level of albumin excretion during exercise is related to the quality of metabolic control; for example, exercise-induced microalbuminuria is more pronounced in newly diagnosed patients, and this abnormality is reversed by insulin treatment. Exercise-induced microalbuminuria generally is not well correlated with the duration of disease and does not predict clinical nephropathy[9]. On the other hand, the contribution of night-time blood pressure (BP) on the onset of nephropathy in diabetic patients is now established[10]. Therefore ambulatory blood pressure monitoring (ABPM) could be proposed as an useful tool for early detection of diabetic nephropathy[11,12]. This study aimed to investigate the relationship between exercise-induced albuminuria and ABPM abnormalities in early detection of diabetic nephropathy in adolescents with T1DM from Cameroon.

MATERIALS AND METHODS
Study subjects
This case-control study was carried out at the National Obesity Center of the Yaoundé Central Hospital, the reference diabetes center in the town. Our population was made of two groups, T1DM adolescents and non-diabetic controls. T1DM patients were aged 12-18 years, with diabetes for at least one year; without proteinuria, with normal office BP and renal function according to the general reference population. Non-diabetic controls were adolescents of general population matched for sex, age and BMI. We excluded patients and controls with an important night activity, those receiving drugs for hypertension or any other drugs able to modify albuminuria, those with contra-indication to exercise or presenting signs of urinary tract infection as well as those having fever and pregnant women.

Procedure and investigations

The procedure was made of an inclusion visit and two exploration visits. Within 2 wk following an information visit, for all eligible participants, we performed a careful clinical exam including BP measurement and a urinary dipstick. We enrolled 40 participants, 20 in each group.

All exploration visits were conducted in the morning between 8:00 and 10:00. After arrival, participants were invited to stay in sitting position for at least five minutes. Then, clinical measurement of BP was done three time using an automated sphygmomanometer Omron HEM-705 CP (Omron Corporation, Tokyo, Japan) placed on the left arm raised itself at the heart level. The average of three measures was considered for analysis. Weight and height were respectively valued to the nearest 0.5 unit using a mechanical scale and a measuring rod and body mass index (BMI in kg/m²) calculated as *weight* (cm)/[*height* (m) × *height* (m)]. A dipstick was done to assess proteinuria and considered positive for at least 1+.

ABPM was carried out on twenty four hours using an automatic portable, light weight monitor device the i-MAPA® CE 004 1.1 TM (High-tech Medical St Louis, Paris) which performs measurements every 15 min during daytime (07:00 to 22:00) and twice an hour during night time defined from 22:00 to 07:00. Device was activated and the two first measures performed in the laboratory to ensure functionality. Detailed information on the operation and use of the device were then given to the participant who then returned to his daily activities. At least 70% of valid measurements were considered for interpretation.

The exercise protocol was developed according to the Hierarchy of individual calibration levels for heart rate and accelerometry to measure physical activity[13]. It was made of 1 km race on a treadmill at 5.8 km/h and was divided in two phases. The first phase was made of a 3 min gathering speed up to 3.2 km/h, followed by an acceleration of 0.33 km/h every 6 min. The second phase was a walking step between 5.2-5.8 km/h on the treadmill.

Albuminuria was calculated using albumin-to-creatinine ratio in order to avoid effect of exercise on urinary concentration and expressed in mg/g. First void urine collection was used for rest albuminuria and a random sample urine was collected within the 20 min following physical exercise to measure exercise-induced albuminuria. Albuminuria or exercise-induced albuminuria was diagnosed on the basis of a urinary albumin excretion rate greater than 20 but less than 200 mg/g[14]. Adverse events such as hypoglycemia during physical exercise or exercise intolerance, were closely monitored.

Statistical analysis

Data acquisition was done by Epi-data 3.1 software and statistical analysis was performed using Stata 12.0 software. Continuous variables are expressed as means with standard deviation (SD) where appropriate,

Table 1 Ambulatory blood pressure measurement of the diabetes and non-diabetes patients

Variables	Type 1 diabetic patients ($n = 20$)	Non-diabetic patients ($n = 20$)	*P* value
24 h BP			
SBP	116 ± 9	111 ± 8	0.06
DBP	69 ± 7	66 ± 5	0.19
PP	48 ± 8	45 ± 5	0.11
Diurnal BP			
SBP	118 ± 10	114 ± 10	0.11
MAP	92 ± 7	89 ± 7	0.15
DBP	71 ± 7	68 ± 6	0.22
Nocturnal BP			
SBP	112 ± 11	106 ± 7	0.06
MAP	85 ± 9	81 ± 6	0.06
DBP	64 ± 9	60 ± 6	0.11

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial blood pressure; PP: Pulse pressure.

and categorical variables as count (percentage). The Spearman rank coefficient was used to test correlations. The χ^2 test and Mann-Whitney rank sum test were used to test associations between qualitative variables and difference between two respectively. A *P* value $\leqslant$ 0.05 was considered statistically significant. The statistical methods of this study were reviewed by Mr. Sontsa.

RESULTS

General characteristics

We enrolled 40 participants, 24 males, average age of 16 ± 2 years. The mean BMI of diabetes patients was 22.6 ± 2.9 kg/m² *vs* 22.7 ± 3.3 kg/m² for non-diabetic. Average duration of diabetes was 4.2 ± 2.8 years with mean glycated hemoglobin of 9.9 ± 2.8. Nine diabetes patients had a family history of hypertension *vs* six in the non-diabetic group.

ABPM measurement of study population

Diabetes participants had lightly higher BP values compared to non-diabetic on every component (Table 1). Thus, 24 h SBP measurement in the diabetic group was 116 ± 9 mmHg *vs* 111 ± 8 mmHg for non-diabetics at borderline of significance (*P* = 0.06) while difference in DBP of two groups was non-significant (69 ± 7 mmHg *vs* 66 ± 5 mmHg; *P* = 0.19). In keeping with that, diurnal BP figures were slightly higher in the diabetic group but with a non-significant difference (SBP: 118 ± 10 mmHg *vs* 114 ± 10 mmHg, *P* = 0.11; DBP: 71 ± 7 mmHg *vs* 68 ± 6 mmHg; *P* = 0.22). One important finding was the elevated night time BP in diabetes adolescents with a borderline significance for SBP (112 ± 11 mmHg *vs* 106 ± 7 mmHg, *P* = 0.06) and MAP (85 ± 9 mmHg *vs* 81 ± 6 mmHg, *P* = 0.06).

Urinary albumin excretion of study population

In adolescents with diabetes, 06/20 (30%) developed abnormal exercise-induced albuminuria but none in the group of adolescents without diabetes. Urinary albumin

Table 2 Comparison of blood pressure values for albuminurics and non albuminurics patients

	UAE < 20 mg/g	UAE > 20 mg/g	*P* value
24 h BP			
SBP	113 ± 9	119 ± 10	0.14
DBP	67 ± 6	70 ± 8	0.51
Diurnal BP			
SBP	116 ± 10	120 ± 10	0.32
DBP	70 ± 5	72 ± 8	0.51
Nocturnal BP			
SBP	108 ± 10	116 ± 10	0.09
DBP	61 ± 8	66 ± 9	0.17

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; UAE: Urinary albumin excretion.

excretion at rest was similar in both groups (5.5 mg/g *vs* 5.5 mg/g, *P* = 0.74). After exercise, we found a significant increase in urinary albumin excretion in diabetes patients as compared to non-diabetics (10.5 mg/g *vs* 5.5 mg/g, *P* = 0.03).

Relation between BP profile and albuminuria at rest and after exercise

We compared diabetes adolescents presenting exercise-induced albuminuria after exercise to those without albuminuria (Table 2). We found that diabetes patients with exercise-induced albuminuria had higher but non-significant nighttime SBP figures than those exercise-induced albuminuria (116 mmHg *vs* 108 mmHg, *P* = 0.09) while DBP were similar. In contrast, 24 h SBP and DBP were similar in both as well as diurnal SBP and DBP.

DISCUSSION

This study aimed to investigate the relationship between exercise-induced albuminuria and circadian BP abnormalities revealed by ABPM in non proteinuric T1DM adolescents. In order to achieve this objective, we compared young T1DM patients to non-diabetic matched controls. We found that nocturnal SBP of diabetic patients was slightly higher than that of non-diabetics as well as 24 h SBP with borderline significance. Most T1DM studies on albuminuria disease have been done in Caucasians[14-17]. This study confirms these findings in Africans. This increase in nocturnal SBP values and 24 h SBP already found by others studies suggest the existence in this group of probable subclinical kidney injuries. Indeed, it was demonstrated that diabetes patients with kidney injury or subclinical diabetic nephropathy had a tendency to higher BP than the general population[14-18]. Similarly, diabetes patients in our study have a tendency to increased nocturnal BP figures in comparison to non-diabetics leading to a reduction in the difference of day-night BP evaluated by dipping[19,20]. This anomaly is found more frequently in diabetes patients compared than in the general population and is attributed to the presence of

kidney damage, still subclinical, but already leading to an increase in renal and cardiovascular risk[18]. Thus, the studies comparing individuals with impaired nocturnal decline in BP and those with normal nocturnal BP have revealed that individuals with insufficient decrease of BP and therefore higher values of BP during the night will present in future monitoring a more rapid degradation of renal function marked by a significant decrease in creatinine clearance[21]. In the same sense, these studies did not find any difference between daytime BP as well as diastolic BP which was also to be the case in our study where daytime BP were similar in both groups of participants[18,20]. However, unlike these studies, we found 24 h BP figures slightly higher in diabetes individuals but still of borderline significance. This could be attributed to the impact of nighttime BP on the 24 h BP and would be a reflection of the nocturnal difference since for similar diurnal BP, if the nocturnal BP is elevated in one group, then it becomes logical that the 24 h BP which is the average daytime and nighttime BP appears to be also more elevated.

Secondly, our study showed that for similar or even identical values of albuminuria at rest, diabetes patients having an increase in nocturnal BP and therefore probable subclinical kidney injuries had a significantly increase in exercise-induced albuminuria in comparison to non-diabetic individuals. This suggests that exercise-induced albuminuria increases with the existence of renal alterations revealed by abnormal nocturnal BP and therefore could be used to detect patients with these abnormalities. This finding support the assumption that exercise-induced albuminuria could serve as a marker of early diabetic renal injuries and allow detection or at least help to suspect the existence of subclinical diabetic nephropathy still undetectable by albuminuria at rest. This had been suggested in 1995 by O'Brien who found during a prospective follow-up on a half-decade that patients having abnormal exercise-induced albuminuria were those who would develop a clinical albuminuria at rest and therefore faster diabetic nephropathy[22-25]. But to the best of our knowledge, nobody has so far studied the relationship between exercise-induced albuminuria and nocturnal abnormalities of BP in type 1 diabetes patients. This first finding then proves very encouraging since it opens the way to new opportunities and show new research fields to explore.

Finally, we compared the diurnal and nocturnal BP values of patients who developed exercise-induced albuminuria to those of other participants without this abnormality. We found that patients with exercise-induced albuminuria had higher non-significant figures of BP during the night than those without this abnormality. These data support the hypothesis emitted above that exercise induced-albuminuria could be used to identify T1DM patients with abnormal nocturnal BP and therefore at risk of developing diabetic nephropathy or already presenting subclinical damage due to diabetic nephropathy. However, these findings casualty refer to other studies on the subject with larger population study

and ideally with a prospective follow-up in order to clearly establish the link between exercise-induced albuminuria and renal prognosis and cardiovascular evaluated by circadian BP on ABPM and especially nocturnal BP abnormalities in T1DM[26-28].

In summary, T1DM patients having an increase in nocturnal BP exhibit an increase exercise-induced albuminuria and patients developing abnormal exercise-induced albuminuria have higher figures of nocturnal BP than others. These findings strongly suggest that exercise-induced albuminuria could to be use identify diabetes patients with subclinical renal damage, therefore it would be useful in the early diagnosis of nephropathy in T1DM.

ACKNOWLEDGMENTS

COMMENTS

Background

Nocturnal abnormalities of blood pressure are correlated with incipient diabetes nephropathy in type 1 diabetes adolescents, but relation with exercised induced-albuminuria has not been investigated yet. Few studies have been conducted on diabetic nephropathy in Africans adolescents.

Research frontiers

Studies on diabetic nephropathy in Africans adolescents are scarce. These data are important to determine the tie between exercise-induced albuminuria and nocturnal blood pressure abnormalities in type 1 diabetes adolescents and the possibility to use it as an earlier marker for diabetes nephropathy.

Innovations and breakthroughs

The authors confirm data of Caucasians studies suggesting that most type 1 diabetes adolescents developed diabetes nephropathy after five years. This study was the first investigating the relationship between exercise-induced albuminuria and ambulatory blood pressure measurement measurements in type 1 diabetes adolescents in the search of early markers of diabetic nephropathy.

Applications

This study shows that there is a relation between exercised-induced albuminuria and nocturnal abnormalities of circadian blood pressure suggesting that exercised-induced albuminuria could be useful as clinical marker for blunted night-time in type 1 diabetes adolescents.

Peer-review

This is a nice study and well done, the topic is clear and the conclusion is novel.

REFERENCES

1   Chiarelli F, Verrotti A, Mohn A, Morgese G. The importance of microalbuminuria as an indicator of incipient diabetic nephropathy: therapeutic implications. *Ann Med* 1997; **29**: 439-445 [PMID: 9453292 DOI: 10.3109/07853899708999374]

2   Bennett PH. 'Microalbuminuria' and diabetes: a critique--assessment of urinary albumin excretion and its role in screening for diabetic nephropathy. *Am J Kidney Dis* 1989; **13**: 29-34 [PMID: 2912062 DOI: 10.1016/S0272-6386(89)80111-8]

3   Lehmann R, Spinas GA. [Diabetic nephropathy: significance of microalbuminuria and proteinuria in Type I and Type II diabetes mellitus]. *Praxis* (Bern 1994) 1995; **84**: 1265-1271 [PMID: 7491450]

4   Perkins BA, Krolewski AS. Early nephropathy in type 1 diabetes: a new perspective on who will and who will not progress. *Curr Diab Rep* 2005; **5**: 455-463 [PMID: 16316598 DOI: 10.1007/s11892-005-0055-7]

5   Steinke JM, Mauer M. Lessons learned from studies of the natural history of diabetic nephropathy in young type 1 diabetic patients. *Pediatr Endocrinol Rev* 2008; **5** Suppl 4: 958-963 [PMID: 18806710]

6   Taboga C, Tonutti L, Noacco C. Effects of physical activity on microalbuminuria in type 1 diabetics without nephropathy. *G Clin Med* 1990; **71**: 569-572 [PMID: 2289652]

7   Feldt-Rasmussen B, Baker L, Deckert T. Exercise as a provocative test in early renal disease in type 1 (insulin-dependent) diabetes: albuminuric, systemic and renal haemodynamic responses. *Diabetologia* 1985; **28**: 389-396 [PMID: 4043581 DOI: 10.1007/BF00280880]

8   Mogensen CE. Microalbuminuria as a predictor of clinical diabetic nephropathy. *Kidney Int* 1987; **31**: 673-689 [PMID: 3550239 DOI: 10.1038/ki.1987.50]

9   Garcia C, Mayaudon H, Bordier L, Le Berre JP, Dupuy O, Bauduceau B. Role of nocturnal blood pressure in the onset of diabetic nephropathy. *Arch Mal Coeur Vaiss* 2007; **100**: 668-672 [PMID: 17928773]

10   Benhamou PY, Halimi S, De Gaudemaris R, Boizel R, Pitiot M, Siche JP, Bachelot I, Mallion JM. Early disturbances of ambulatory blood pressure load in normotensive type I diabetic patients with microalbuminuria. *Diabetes Care* 1992; **15**: 1614-1619 [PMID: 1468293 DOI: 10.2337/diacare.15.11.1614]

11   Garcia C, Mayaudon H, Bordier L, Berre JL, Dupuy O, Bauduceau B. Responsabilité de la pression artérielle nocturne dans l'apparition d'une néphropathie chez les diabétiques. Available from: URL: http//http://www.em-consulte.com/en/article/130277

12   Brage S, Ekelund U, Brage N, Hennings MA, Froberg K, Franks PW, Wareham NJ. Hierarchy of individual calibration levels for heart rate and accelerometry to measure physical activity. *J Appl Physiol* (1985) 2007; **103**: 682-692 [PMID: 17463305]

13   Darcan S, Goksen D, Mir S, Serdaroglu E, Buyukinan M, Coker M, Berdeli A, Köse T, Cura A. Alterations of blood pressure in type 1 diabetic children and adolescents. *Pediatr Nephrol* 2006; **21**: 672-676 [PMID: 16568306 DOI: 10.1152/japplphysiol.00092.2006]

14   Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, Patel A, Cass A, Neal B, Poulter N, Mogensen CE, Cooper M, Marre M, Williams B, Hamet P, Mancia G, Woodward M, Macmahon S, Chalmers J. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol* 2009; **20**: 1813-1821 [PMID: 19443635 DOI: 10.1681/ASN.2008121270]

15   Poulsen PL, Ebbehøj E, Nosadini R, Fioretto P, Deferrari G, Crepaldi G, Mogensen CE. Early ACE-i intervention in microalbuminuric patients with type 1 diabetes: effects on albumin excretion, 24 h ambulatory blood pressure, and renal function. *Diabetes Metab* 2001; **27**: 123-128 [PMID: 11353877]

16   Poulsen PL, Ebbehøj E, Mogensen CE. Lisinopril reduces albuminuria during exercise in low grade microalbuminuric type 1 diabetic patients: a double blind randomized study. *J Intern Med* 2001; **249**: 433-440 [PMID: 11350567 DOI: 10.1046/j.1365-2796.2001.00821.x]

17   Poulsen PL, Ebbehøj E, Arildsen H, Knudsen ST, Hansen KW, Mølgaard H, Mogensen CE. Increased QTc dispersion is related to blunted circadian blood pressure variation in normoalbuminuric type 1 diabetic patients. *Diabetes* 2001; **50**: 837-842 [PMID: 11289050 DOI: 10.2337/diabetes.50.4.837]

18   Hansen KW, Poulsen PL, Mogensen CE. Ambulatory blood pressure and abnormal albuminuria in type 1 diabetic patients. *Kidney Int Suppl* 1994; **45**: S134-S140 [PMID: 8158882]

19   Cohen CN, Albanesi FM, Gonçalves MF, Gomes MB. Ambulatory blood pressure monitoring and microalbuminuria in normotensive subjects with insulin-dependent diabetes mellitus. *Arq Bras Cardiol* 2000; **75**: 195-204 [PMID: 11018805 DOI: 10.1590/S0066-782X2000000900001]

20   Sochett EB, Poon I, Balfe W, Daneman D. Ambulatory blood pressure monitoring in insulin-dependent diabetes mellitus adolescents with

and without microalbuminuria. *J Diabetes Complications* 1998; **12**: 18-23 [PMID: 9442810 DOI: 10.1016/S1056-8727(97)00050-0]

21   **Pańkowska E**, Golicka D. Changes in blood pressure and methods of blood pressure monitoring in patients with type-1 diabetes. *Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw* 2005; **11**: 33-37 [PMID: 15850536]

22   **Hansen KW**, Poulsen PL, Mogensen CE. 24-h blood pressure recordings in type I diabetic patients. *J Diabetes Complications* 1995; **9**: 237-240 [PMID: 8573736 DOI: 10.1016/1056-8727(95)80011-3]

23   **Shalaby NM**, Shalaby NM. Study of ambulatory blood pressure in diabetic children: prediction of early renal insult. *Ther Clin Risk Manag* 2015; **11**: 1531-1537 [PMID: 26491340 DOI: 10.2147/TCRM.S87751]

24   **Farmer CK**, Goldsmith DJ, Quin JD, Dallyn P, Cox J, Kingswood JC, Sharpstone P. Progression of diabetic nephropathy--is diurnal blood pressure rhythm as important as absolute blood pressure level? *Nephrol Dial Transplant* 1998; **13**: 635-639 [PMID: 9550639

DOI: 10.1093/ndt/13.3.635]

25   **O'Brien SF**, Watts GF, Powrie JK, Shaw KM. Exercise testing as a long-term predictor of the development of microalbuminuria in normoalbuminuric IDDM patients. *Diabetes Care* 1995; **18**: 1602-1605 [PMID: 8722059 DOI: 10.2337/diacare.18.12.1602]

26   **Marshall SL**, Edidin DV, Arena VC, Becker DJ, Bunker CH, Gishoma C, Gishoma F, LaPorte RE, Kaberuka V, Ogle G, Sibomana L, Orchard TJ. Glucose control in Rwandan youth with type 1 diabetes following establishment of systematic, HbA1c based, care and education. *Diabetes Res Clin Pract* 2015; **107**: 113-122 [PMID: 25458328 DOI: 10.1016/j.diabres.2014.09.045]

27   **Gonzalez Suarez ML**, Thomas DB, Barisoni L, Fornoni A. Diabetic nephropathy: Is it time yet for routine kidney biopsy? *World J Diabetes* 2013; **4**: 245-255 [PMID: 24379914 DOI: 10.4239/wjd.v4.i6.245]

28   **American Diabetes Association**. Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]