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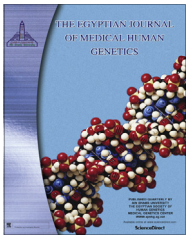

ORIGINAL ARTICLE

Soluble receptor for advanced glycation end products (sRAGE) and carotid intima-media thickness (CIMT) in type 1 diabetes Mellitus: Possible association with diabetic vascular complications

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KEYWORDS

Type 1 diabetes mellitus;
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Abstract *Background:* Advanced glycation end products (AGEs) are a heterogeneous and complex group of biochemical compounds, resulting from nonenzymatic glycation and oxidation of protein, nucleic acids, and lipids.

Aim of the study: To assess sRAGE and CIMT in patients with T1DM and their relation to glycemic control and diabetic vascular complications.

Patients & methods: This study included 60 patients with mean age of 14.4 ± 3.4 years. They were subdivided into complicated and non complicated groups according to the presence of microvascular complications. Thirty age and sex matched controls were included. Patients with disease duration less than 5 years, connective tissue disease, liver dysfunction, or apparent cardiovascular disease and those on lipid lowering agents were excluded. Laboratory investigations included; HbA1c%, urinary albumin excretion (UAE), fasting lipid profile and sRAGE. Mean CIMT was measured by dopplex ultrasound.

Abbreviations: sRAGE, soluble receptor for advanced glycation end products; CIMT, carotid intima-media thickness; AGEs, advanced glycation end products; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index; UAE, urinary albumin excretion; T1DM, type 1 diabetes mellitus

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Results: Patients had higher sRAGE (1765.0 ± 451.0 pg/ml) ($p < 0.001$) especially the non complicated group ($p = 0.18$). It was directly correlated to HDL ($r = 0.3$, $p = 0.012$). Patients had increased CIMT (0.57 ± 0.14 mm) ($p < 0.001$) with 13.3% having carotid wall abnormalities. CIMT was directly correlated to age, weight, BMI, systolic and diastolic blood pressures, UAE, cholesterol and LDL ($p < 0.05$) and inversely correlated to HDL ($p < 0.05$). Neither CIMT nor sRAGE were correlated to glycemic control or disease duration.

Conclusion: Patients with T1DM are at risk of increased CIMT with a concomitant increase in sRAGE which may be a therapeutic target for the prevention of diabetic vascular complications.

1. Introduction

Advanced glycation end products (AGEs) represent a family of proteins, peptides, amino acids, nucleic acids and lipid adducts formed by the reaction of carbonyl compounds derived directly or indirectly from glucose, ascorbic acid and other metabolites such as methylglyoxal. AGEs formation in diabetes is of growing importance for their role as markers and potential culprits of diabetic complications, in particular retinopathy, nephropathy and neuropathy [1]. Receptor for AGEs (RAGE) is a cell-bound receptor of the immunoglobulin superfamily, which may be activated by a variety of proinflammatory ligands. AGEs bind to RAGE, thereby leading to activation of a range of inflammatory and fibrotic pathways causing tissue injury [2]. Soluble RAGE (sRAGE), arising from ectodomain shedding of membrane RAGE and secretion of spliced variants, counteracts the pathogenic effect of AGE-RAGE signaling by acting as a decoy of AGEs [3]. Investigating AGEs–RAGE axis may facilitate spiraling toward pathology of many fronts including cardiovascular disease (CVD) development [4]. The aim of this study is to evaluate sRAGE level in children and adolescents with type 1 diabetes mellitus and its possible relation to glycemic control, diabetic vascular complications as well as carotid intima-media thickness as a marker of atherosclerosis.

2. Patients

The present study is a case control study. It was conducted at the Pediatric Diabetes Clinic, Children's Hospital; Ain Shams University in the period from April 2011 to April 2012. It included 60 patients with type 1 diabetes mellitus of more than 5 years duration from those who regularly attend the clinic. Their ages ranged from 6 to 18 years with the mean age of 14.4 ± 3.4 years. There were 40 females and 20 males. Any patient with type 2 diabetes mellitus, BMI more than 95th percentile (according to Egyptian growth charts) [5], patients with malignancy, connective tissue disease, liver dysfunction, renal dysfunction (serum creatinin > 1.2 mg/dl), apparent cardiovascular disease or taking any oral hypoglycemic, antiplatelet or lipid lowering medications were excluded from the study. Patients were further subdivided into two groups according to the presence of microvascular complications; **Group I:** Thirty patients with diabetic microvascular complications (nephropathy $n = 10$, retinopathy $n = 6$ and/or neuropathy $n = 24$). **Group II:** Thirty patients without diabetic microvascular complications. Thirty age and sex matched healthy individuals were included as a control group. A written informed consent was taken from all patients or their legal guardians. The work is carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Data collected from patients included; demographic data, disease duration, insulin type and dose (Unit/kg/day), monitoring of treatment and symptoms suggestive of any diabetic complications. Complete physical examination included; Vital signs, anthropometric measures plotted against Egyptian percentile for age and sex, body mass index (BMI) and sexual maturity rating according to Tanner's classification [6]. Fundus examination was also done.

3. Methods

Laboratory investigations included; Mean random blood glucose by enzymatic method on Hitashi instruments. Glycosylated Hemoglobin (HbA1c%) was calculated using HPLC (High performance liquid chromatography) and the mean value over the last year follow up was calculated [7]. Urinary albumin excretion (UAE) was measured; using the immunoturbidimetric method [8]. Fasting serum lipid profile [cholesterol, triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL)] was done and sRAGE serum level was also estimated by ELISA. Assessment of carotid intima-media thickness by Carotid Dopplex Ultrasound was done at the Ain Shams Radiology Department to estimate; Intimal thickening, wall irregularities and any plaques (either soft, calcified or ulcerated). Color Duplex was used to give an overview of the carotid system to guide the application of the spectral flow at any suspected stenotic site. Sometimes B mode ultrasound was used for better delineation of the region of the pathway.

4. Statistical methods

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 17.0. Descriptive statistics were done for numerical parametric data as mean ± SD (standard deviation) and minimum & maximum of the range and for numerical non parametric data as median (IQR) [1st & 3rd inter-quartile range], while they were done for categorical data as number and percentage. Analysis was done for quantitative variables using independent *t*-test in cases of two independent groups with parametric data and Mann Whitney U in cases of two independent groups with non parametric data. Analysis was done for qualitative data using Chi square test for independent variables while correlations were done using Pearson Correlation for numerical parametric data, and

using spearman rho test for numerical non parametric and categorical data. ROC curve was used to evaluate the value of different tests that differentiate between certain groups. The level of significance was taken with p value < 0.05 being significant, otherwise it is not significant.

5. Results

Patients and controls were matched for age and sex ($p > 0.05$). None of the controls were prepubertal, 30% were early pubertal stage (II, III Tanner classification) and 70% were late pubertal stage (IV, V Tanner classification). On the other hand; 20% of patients were prepubertal, 43.4% were early pubertal and 36.6% were late pubertal ($p = 0.007$). There was no significant difference between patients and controls as regards vital signs ($p > 0.05$). Patients with type 1 DM had significantly increased levels of cholesterol, LDL and triglycerides and lower level of HDL ($p < 0.05$) (Table 1) with no significant difference in lipid profile between the two groups of patients ($p > 0.05$). sRAGE was significantly higher among patients ($p \leqslant 0.001$). Mean CIMT was significantly higher in patients ($p \leqslant 0.001$) (Table 1) especially in males (0.61 mm) compared to females (0.52 mm) ($p = 0.003$). There was no significant difference between males and females as regards CIMT among controls ($p = 0.633$). Four (13.3%) of patients had carotid wall abnormalities in the form of atheroma in the wall causing stenosis or intraintimal cystic lesions compared to none of the controls (Fig. 1).

Both sRAGE and mean CIMT had good value to differentiate between patients and controls. Mean CIMT of 0.52 mm was the best cutoff value to differentiate between patients and controls with low sensitivity (56%) and high specificity (90%) while; sRAGE had 70% sensitivity and 70% specificity to differentiate between patients and controls at a cutoff point of 1475 pg/ml (Fig. 2).

Table 1 Blood pressure values, laboratory and CIMT findings among patients and controls.

	Patients $N = 60$	Controls $N = 30$	Test	p
SBP percentile				
5–95	58(96.7%)	30(100%)	1.023[#]	0.312
>95	2(3.3%)	0(0.0%)		
DBP percentile				
5–95	58(96.7%)	30(100%)	1.023[#]	0.312
>95	2(3.3%)	0(0.0%)		
Cholesterol (mg/dL)	149.4 ± 45.4	124.3 ± 15.8	3.886[^]	**< 0.001**[*]
Triglycerides (mg/dL)	92.2 ± 30.0	61.5 ± 9.1	7.466[^]	**< 0.001**[*]
LDL (mg/dL)	101.1 ± 35.5	69.6 ± 6.8	7.099[^]	**< 0.001**[*]
HDL (mg/dL)	39.6 ± 9.3	50.1 ± 10.3	−5.002[^]	**< 0.001**[*]
sRAGE (pg/ml)	1765 ± 451.0	1408 ± 126.3	5.690[^]	**< 0.001**[*]
Mean CI MT (mm)	0.57 ± 0.14	0.48 ± 0.06	3.39[^]	**< 0.001**[*]
Range	(0.45–1.25)	0.40–0.60)		
Right CI MT (mm)	0.59 ± 0.19	0.48 ± 0.06		
Range	(0.40–1.5)	(0.40–0.60)		
Left CIMT (mm)	0.56 ± 0. 11	0.48 ± 0.05		
Range	(0.40–1.0)	(0.40–0.60)		
Wall abnormalities (n, %)	4 (13.3)	0 (0)		

SBP; Systolic blood pressure. DBP; Diastolic blood pressure. LDL; Low density lipoprotein. HDL; High density lipoprotein. sRAGE; Soluble receptor for advanced glycation end product. CIMT; Carotid intema-media thickness.

[#] Chi square test.

[^] Independent t-test.

[*] Signifies the bold results.

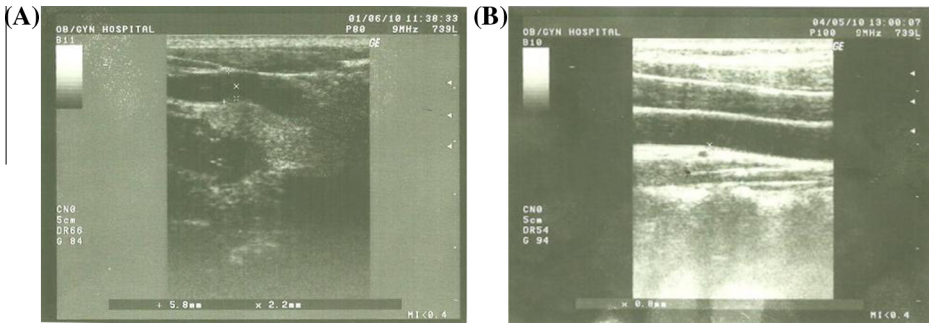

Figure 1 (A) A localized soft atheroma causing 50% stenosis at the CCA lumen. (B) Segmental regional intimal thickening of the right CCA. The localized small intraintimal cystic lesion could represent associated intimal cyst or ulceration.

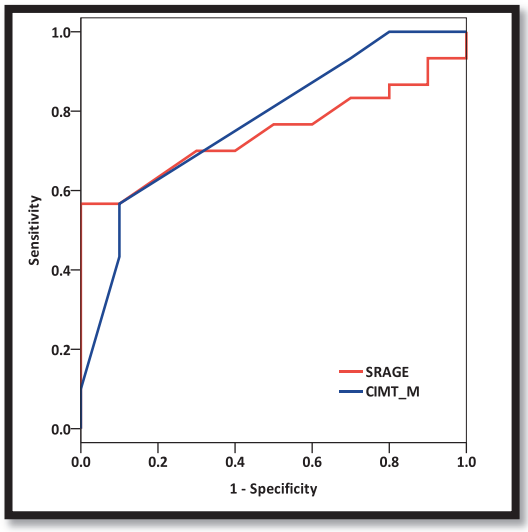

Figure 2 ROC curve for sRAGE and mean CIMT to differentiate between patients and controls [AUC = 0.75 (95% CI:0.65–0.85, $p < 0.001$) and 0.77 (95% CI:0.67–0.87, $p < 0.001$), respectively.

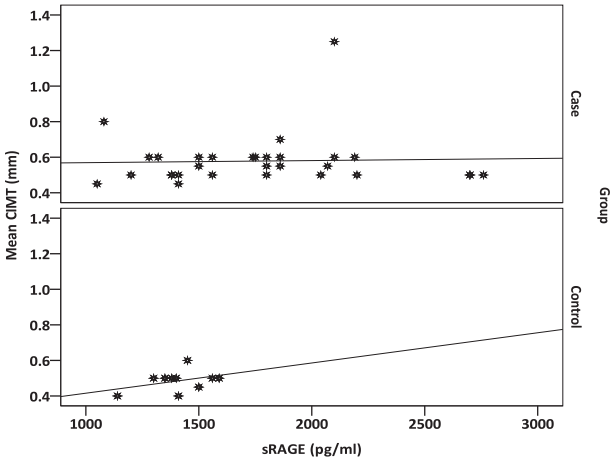

Figure 3 Correlation between S-RAGE and CIMT in patients and controls.

A significant direct correlation between sRAGE and mean CIMT was detected only in the control group ($r = 0.384$, $p = 0.036$).

Mean CIMT was directly correlated to age, weight, BMI, systolic and diastolic blood pressures ($p < 0.05$) among patients, while; a significant direct correlation between sRAGE and age, weight, height and BMI and an inverse correlation between sRAGE and SBP were only detected in controls ($r = -0.562$, $p < 0.001$).

There was a significant direct correlation between mean CIMT and UAE ($r = 0.34$, $p = 0.007$). There was a significant direct correlation between mean CIMT and cholesterol, LDL and a significant inverse correlation between CIMT and HDL in both patients and controls ($p < 0.05$) (Fig. 3). sRAGE was directly correlated to HDL ($r = 0.3$, $p = 0.012$) among patients. Triglyceride was directly correlated to mean CIMT only in controls (Fig. 4 and 5).

There was a significant inverse correlation between mean CIMT and insulin dose ($r = -0.342$, $p = 0.007$) and frequency of monitoring ($r = -0.408$, $p < 0.001$) among patients while; there was no correlation between either CIMT or sRAGE and disease duration ($r = 0.059$, $p = 0.66$ and $r = -0.18$, $p = 0.17$, respectively) or HbA1c% ($r = -012$, $p = 0.35$ and $r = 0.049$, $p = 0.71$, respectively).

There was no significant difference between group I and group II of patients as regards demographic characteristics, tanner score or vital signs ($p > 0.05$). Among group I of patients; 6 (20%) patients had retinopathy, 10 (33.3%) had nephropathy and 24 (80%) had neuropathy.

UAE was significantly higher in group I with microalbuminuria and frank proteinuria detected in 26.7% and 6.7%, respectively compared to none among group II. sRAGE was higher among group II, but this did not reach a statistical significance ($p = 0.18$) (Table 2). Moreover; sRAGE was significantly higher in patients without retinopathy (1810 ± 444.5 pg/ml) than those with retinopathy (1360 ± 319 pg/ml) ($p < 0.05$) while; it was higher among patients with nephropathy (1798 ± 275.9 pg/ml) and those without neuropathy (1835 ± 446 pg/ml), but this did not reach statistical significance ($p > 0.05$).

Mean CIMT was higher in group I but this did not reach statistical significance ($p = 0.33$) (Table 2). There was no significant difference between patients with and without retinopathy, nephropathy or neuropathy as regards CIMT ($p > 0.05$).

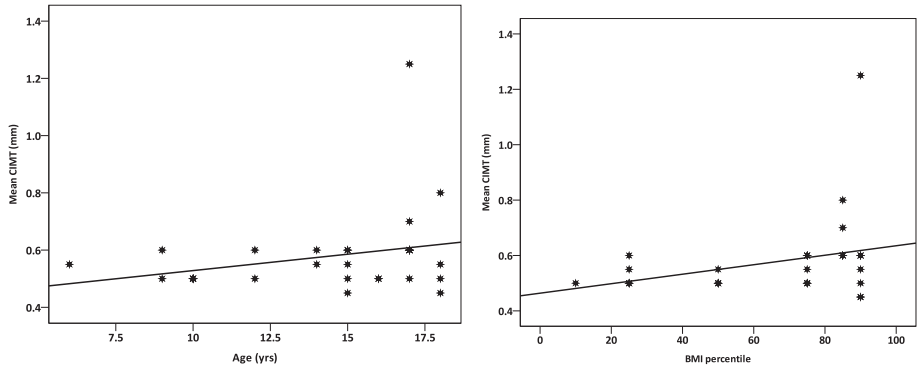

Figure 4 Correlation between mean CIMT with age and BMI percentiles in patients.

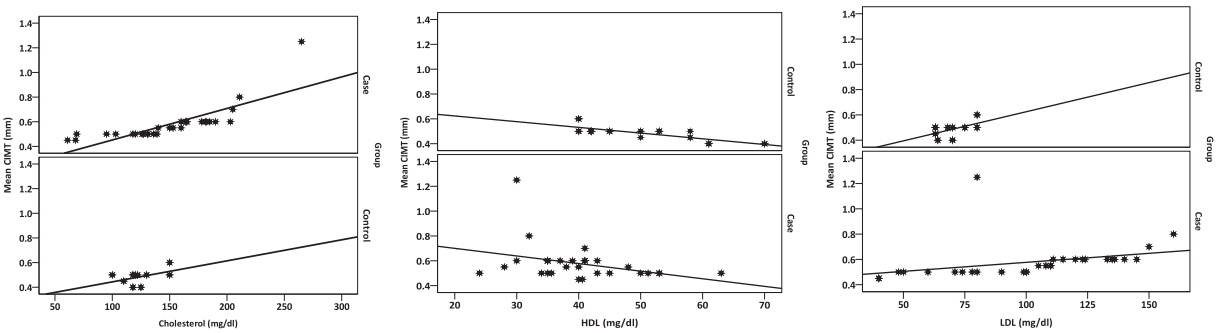

Figure 5 Correlation between mean CIMT and lipid profile in patient and control groups.

Table 2 Laboratory and CIMT findings among patients' groups.

	Group I (n = 30)	Group II (n = 30)	Test value	p
sRAGE (pg/ml)	1686.7 ± 432.7	1844.0 ± 465.3	−1.356ˆ	0.180
Urinary albumin excretion (μg/mg)	25.4 (20.0–43.0)	20.0 (16.0–22.0)	−3.293&	**< 0.001***
Urinary albumin excretion (μg/mg)				
< 30	20 (66.7%)	30 (100.0%)	12.00#	**0.002***
30–300	8 (26.7%)	0 (0.0%)		
> 300	2 (6.7%)	0 (0.0%)		
Mean CIMT(mm)	0.60 ± 0.19	0.56 ± 0.08	0.976ˆ	0.333
Wall abnormalities	1 (3.3%)	3 (10.0%)	1.071#	0.301

sRAGE; soluble receptor for advanced glycation end product. CIMT; carotid intema-media thickness.
ˆ Independent t-test.
& Mann Whitney test.
# Chi square test.
* Signifies the bold results.

Both sRAGE and mean CIMT had no value to differentiate between group I and group II (AUC = 0.4 and 0.51, respectively).

6. Discussion

Diabetes may render the arterial wall more susceptible to harmful influences of circulating LDL cholesterol [9]. Diabetics with endothelial dysfunction appear to be at particular risk for developing early structural atherosclerotic changes [10].

In our study; total cholesterol, low density lipoprotein, triglycerides were significantly higher in patients than controls while high density lipoprotein (HDL) was significantly lower. This is in agreement with other studies [11]. Others reported no difference in lipid profile between diabetics and controls [12].

Our patients displayed significantly higher sRAGE levels than controls. Similar findings were reported by other studies [13]. In addition; a French study investigating a small group of patients with type 1 diabetes mellitus found elevated levels of sRAGE in diabetic patients as compared to controls [14].

In contrast to our results Grossin et al. reported no significant difference in sRAGE level between controls and patients with type 1 diabetes but without complications [15], while; Basta et al. proved that plasma levels of sRAGE decreased in diabetic patients [16].

sRAGE level was higher among the uncomplicated group of patients despite that this did not reach a statistical significance; its level was higher among those without retinopathy or neuropathy suggesting a protective role; while it was higher among those with nephropathy. Similar finding was reported by Abdel-Aziz and El-Okely [17]. Nin et al. reported that sRAGE levels tended to be higher in the presence and across the levels of severity of retinopathy and nephropathy [18]. However; a number of studies have suggested that administration of sRAGE is protective against diabetic complications [19–21]. Multiple studies indicated that RAGE is increased in diseases of the kidney, including diabetes [22], as well in advanced kidney disease. It is not clear if such high levels of sRAGE were related to decreased clearance or for stimulation by environmental toxic factors [23].

The blockade of the AGE-RAGE axis by administration of sRAGE ameliorates neuronal dysfunction and reduces the development of cellular capillaries and pericyte ghosts in experimental diabetic retinopathy [24]. Furthermore; Kaji et al. have shown that attenuation of the RAGE axis with injection of sRAGE inhibits retinal leukostasis and retinal barrier breakdown in the diabetic mice which are accompanied by decreased expression of vascular endothelial growth factor (VEGF) and intercellular cell adhesion molecule (ICAM) in the retina [25]. On the other hand; Ng et al. reported that the increased circulating level of plasma sRAGE would not likely reduce the rate of DR progression in type 2 DM patients [26].

In the current study there was a significant direct correlation between sRAGE and HDL in patients while; Katakami et al. found that sRAGE had no significant correlation with triglycerides or HDL, but it was inversely correlated with total

cholesterol. Also; they reported that sRAGE had no significant correlation with SBP in patients [27].

A significant positive correlation was found between sRAGE and CIMT only in controls. Similar results were reported by others [16]. Their observation suggested that higher levels of sRAGE may be a biomarker of a high degree of vascular affections in non diabetic patients with coronary artery disease.

Others revealed that continuous low levels of circulating sRAGE were determinants of the progression of mean CIMT independently of conventional risk factors and that plasma levels of sRAGE were positively associated with macrovascular complications [18].

Similar to our finding; Yamagishi et al. reported that age significantly increased in proportion to the increasing levels of sRAGE in non diabetic individuals [13], however; we observed no significant correlation with age, disease duration or HbA1c% in patients. This is in agreement with Katakami et al. and in contrast to Basta et al. who reported that plasma sRAGE was inversely associated with HbA1c% [16,27].

In the present study, diabetic patients displayed a significant increase in mean CIMT compared to the normal control. Similar results were reported in other studies [11,12,27]. Diabetes predisposes to increased subclinical atherosclerosis at a very early age but no plaque formations were observed in any of the studied children [28].

This is in contrast to our findings, whereas; 4 (13.3%) of the studied patients had carotid wall abnormalities in the form of atheroma in the wall causing stenosis, and intraintimal cystic lesions.

Similar to our finding; Margeirsdottir et al. found that elevated CIMT among diabetic patients was the most prominent in boys [11]. In contrast Jarvisalo et al. found no sex difference in CIMT between children with diabetes and controls [28].

CIMT was directly correlated with age of patients, similar finding was reported by many studies [12,29]. In contrast; Katakami et al. found no significant correlation between CIMT and age in patients with type 1 diabetes [27].

Despite statistically insignificant; higher levels of CIMT were detected among complicated patients. Many other studies reported higher CIMT among diabetic patients with microvascular complications indicating the association of diabetic microangiopathy and macroangiopathy [12,30].

Similar to our finding; Gül et al. found that CIMT was positively correlated with urinary albumin excretion, a sensitive marker of diabetic nephropathy, while; Dalla Pozza et al. failed to find such correlation [12,31].

The direct correlation between mean CIMT with SBP, DBP, cholesterol and LDL in our patients was supported by many other studies [29,31,32], while; others denied such correlations [11,12].

In agreement with our results; Margeirsdottir et al. showed no association between IMT and duration of diabetes [11], while; others found a direct correlation between CIMT and duration of diabetes [12,28].

There was no significant correlation between mean CIMT and HbA1c% [11,12,28]. Dall Pozza et al. revealed a positive correlation between mean CIMT and HbAlc% [31].

Improved blood glucose control obtained by intensive insulin treatment is associated with delayed atherosclerosis development and less cardiovascular events [29].

7. Conclusion

Patients with type 1 diabetes mellitus are at risk of atherosclerosis marked by elevated CIMT which is related to increased age, BMI, blood pressures, diabetic nephropathy and dyslipidemia. It is not related to disease duration or metabolic control. Concomitant increase in sRAGE especially among the uncomplicated group of patients may suggest a therapeutic role of sRAGE in the prevention of diabetic vascular complications.

8. Funding

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9. Conflict of interests

No conflict of interests to be declared.

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