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ORIGINAL ARTICLE

Basic Study

Expression of *matrix metalloproteinase-11* is increased under conditions of insulin resistance

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Abstract

AIM

To investigate *matrix metalloproteinase-11* (*MMP-11*) expression in adipose tissue dysfunction, using *in vitro* and *in vivo* models of insulin resistance.

METHODS

Culture of mouse 3T3-L1 preadipocytes were induced to differentiation into mature 3T3-L1 adipocytes. Cellular insulin resistance was induced by treating differentiated cultured adipocytes with hypoxia and/or tumor necrosis factor (TNF)-α, and transcriptional changes were analyzed in each condition thereafter. For the *in vivo* studies, *MMP-11* expression levels were measured in white adipose tissue (WAT) from C57BL/6J mice that underwent low fat diet or high-fat feeding in order to induce obesity and obesity-related insulin resistance. Statistical analysis was carried out with GraphPad Prism Software.

RESULTS

MMP-11 mRNA expression levels were significantly higher in insulin resistant 3T3-L1 adipocytes compared to control cells (1.46 ± 0.49 *vs* 0.83 ± 0.21, respectively;

P < 0.00036). The increase in *MMP-11* expression was observed even in the presence of TNF-α alone (3.79 ± 1.11 *vs* 1 ± 0.17, *P* < 0.01) or hypoxia alone (1.79 ± 0.7 *vs* 0.88 ± 0.1, *P* < 0.00023). The results obtained in *in vitro* experiments were confirmed in the *in vivo* model of insulin resistance. In particular, *MMP-11* mRNA was upregulated in WAT from obese mice compared to lean mice (5.5 ± 2.8 *vs* 1.1 ± 0.7, respectively; *P* < 3.72E-08). The increase in *MMP-11* levels in obese mice was accompanied by the increase in typical markers of fibrosis, such as collagen type Ⅵ alpha 3 (*Col6α3*), and fibroblast-specific protein 1.

CONCLUSION

Our results indicate that dysregulation of *MMP-11* expression is an early process in the adipose tissue dysfunction, which leads to obesity and obesity-related insulin resistance.

Key words: Metalloproteinase-11; Insulin resistance; Type 2 diabetes; Fibrosis; Hypoxia; Tumor necrosis factor-α; Inflammation

Core tip: 3T3-L1 mature adipocytes are widely used as a cellular model of obesity. We treated 3T3-L1 adipocytes with tumor necrosis factor-α and/or hypoxia for 24 h to induce insulin resistance. *Matrix metalloproteinase-11* (*MMP-11*) expression levels were upregulated in insulin resistant adipocytes, as compared to untreated control cells. This observation was confirmed *in vivo*, in white adipose tissue from insulin-resistant obese mice. Therefore, our results suggest that *MMP-11* could play a role in the dysfunction of adipose tissue, which leads to insulin resistance and type 2 diabetes. Further work is necessary to understand better the functional role of *MMP-11* in this context.

Arcidiacono B, Chiefari E, Laria AE, Messineo S, Bilotta FL, Britti D, Foti DP, Foryst-Ludwig A, Kintscher U, Brunetti A. Expression of *matrix metalloproteinase-11* is increased under conditions of insulin resistance. *World J Diabetes* 2017; 8(9): 422-428 Available from: URL: http://www.wjgnet.com/1948-9358/full/v8/i9/422.htm DOI: http://dx.doi.org/10.4239/wjd.v8.i9.422

INTRODUCTION

Insulin resistance is a pathological condition in which insulin target tissues fail to properly respond to insulin. It is more frequently associated with overweight and obesity, and constitutes a prominent feature of type 2 diabetes (T2D) and the metabolic syndrome[1,2]. In the past decades, research findings have substantially improved our understanding of the pathophysiology of insulin resistance, thanks to the identification of new genetic defects and molecular events that underlie the abnormalities that occur in both peripheral insulin action and insulin secretion[3-7]. Particular interest in this field has been devoted to the investigation of obesity, as it is considered the major risk factor for insulin resistance, which leads to the development of T2D and other obesity-associated insulin resistant states. Therefore, because of the parallel increasing prevalence of obesity and metabolic diseases, much research has been recently focused on the role of adipose tissue, previously considered as a fat storage tissue only. Evidence from the last years has established the involvement of adipose tissue in the production of hormones and numerous other biologically active molecules collectively called "adipokines" that are implicated in metabolic and inflammatory pathways[8]. Based on the new view of adipose tissue as an endocrine organ, new insights have been gained over the last years into the mechanisms linking adipose tissue to insulin resistance, although the entire sequelae of events that initially trigger adipose tissue dysfunction still remain poorly defined.

The *matrix metalloproteinase-11* (*MMP-11*; also known as stromelysin-3) is a proteinase *enzyme* that belongs to the family of metalloproteinases, and is involved in remodeling and degradation of extracellular matrix (ECM). Unlike other MMPs that are secreted in an inactive form to be then activated extracellularly, *MMP-11* is maturated in the Golgi's apparatus and secreted in an active form[9]. *MMP-11* is implicated in tissue remodeling during embryogenesis, tissue involution and metamorphosis, and in biological process of tissue repair after trauma[10]. In addition, as shown in *in vivo* studies, *MMP-11* plays a role in tumor development and progression. In particular, cancer cells, by inducing the adjacent fat cells to express *MMP-11*, may contribute to modify the ECM, thereby favoring cancer cell migration into the connective tissue, during the initial step of the invasive process[11]. In this regard, the involvement of *MMP-11* in certain types of cancers (*i.e.,* breast, colorectal and lung) has been confirmed in clinical studies, in which it has also been established that higher expression of *MMP-11* correlates with tumor aggressiveness and lower survival rate among affected patients[12]. However, although the numerous studies carried out up to date, both *in vitro* and *in vivo*, the precise molecular target(s) of *MMP-11* and their specific role in normal and pathological conditions have not yet been clarified. It has been demonstrated that active *MMP-11* is primarily responsible for the digestion of collagen Ⅳ and Ⅵ, fibronectin, alpha 2-macroglobulin and insulin-like grow factor binding protein 1 (IGFBP1)[13,14]. However, all these substrates are not specific for this enzyme as they can be also cleaved by other MMPs.

In the present study, we investigated the expression of *MMP-11* in an *in vitro* model of insulin resistance, and in a murine diet-induced model of obesity.

MATERIALS AND METHODS

Cell culture

3T3-L1 mouse preadipocytes were cultured in Dulbecco's modified Eagle's medium (DMEM) supplied with 10% fetal bovine serum, 100 U/mL penicillin and 100 μg/mL

streptomycin and maintained at 37 ℃ in 5% CO_2 humidified atmosphere. As soon as the confluence was reached, cells were induced to differentiate as reported previously[15,16]. In brief, the differentiation process was started through the addition of 500 μmol/L of 3-isobutyl-1-methylxanthine (IBMX), 1 μmol/L of dexamethasone and 1 μg/mL of insulin. The cells were incubated for three days in the differentiation medium, followed by 2 d of treatment with DMEM containing 1 μg/mL insulin. The medium was replaced every two days and experiments were performed using day 8 to day 12 mature adipocytes.

Induction of insulin resistance in vitro

To induce insulin resistance, mature 3T3-L1 adipocytes were treated with 2.5 nmol/L tumor necrosis factor (TNF)-α, and simultaneously incubated in hypoxic conditions for 24 h[17]. Before inducing insulin resistance, 3T3-L1 adipocytes were cultured in DMEM at low glucose concentration (1 g/L) and 0.5% BSA, plus rh-TNF-α, and put in the hypoxic chamber (1% O_2, 5% CO_2) at 37 ℃ for 24 h. Control cells were incubated in the same conditions, but in normal atmosphere (21% O_2).

Total RNA isolation and reverse transcription

Total RNA was extracted from white adipose tissue (WAT) and 3T3-L1 cells, using Trizol reagent (Invitrogen), according to the manufacturer's instructions[18]. RNA concentration was measured by a NanoDrop spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, United States), and its quality confirmed on agarose gel. One microgram of RNA sample was used for cDNA synthesis, using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems), in the presence of the following reagents: 10 × RT Buffer, 100 mmol/L dNTP mix, 10 × RT Random Primers and 0.50 U/μL Multiscribe Reverse Transcriptase. The cDNA thermal-profile was 25 ℃ for 10 min, 37 ℃ for 120 min and the enzyme was inactivated at 85 ℃ for 5 min.

Quantitative PCR

Relative quantification was performed to measure *MMP-11* expression, using a real-time thermocycler (Eppendorf Mastercycler ep realplex ES). One microliter of cDNA and 0.2 μmol/L of each primers were mixed with SYBR Green RealMasterMix (Eppendorf). S9 and 18S were used as internal reference controls. Primers were designed for mouse *MMP-11*, S9 and 18S, using the Primer3web version 4.0[19,20], according to sequences from the GeneBank database. Amplification conditions were: 2 min at 95 ℃ and three step-cycle of 95 ℃ for 15 s, 58 ℃ for 20 s and 68 ℃ for 20 s, for a total of 40 cycles.

Western blot

Cells were lysed as described previously[21]. Cellular protein (20 μg) was resolved on 10% SDS-PAGE, transferred to PVDF membrane (Immobilon-PSQ 0.2 μm Millipore ISEQ00010), blotted for 2 h with blocking solution (5% non-fat dry milk), then incubated overnight at 4 ℃ with primary antibody against *MMP-11* (Santa Cruz sc8836 dilution 1:1000), followed by incubation for 1 h at room temperature with a secondary antibody linked to horseradish peroxidase. Immune complexes were visualized by enhanced chemiluminescence (ECL, Amersham).

Animals

Five week-old male C57BL/6J mice were housed in individual cages and maintained on 12 h light-dark cycle with controlled temperature (25 ℃) and humidity (50% ± 5%), and with free access to water. To induce obesity, ten mice were fed ad libitum with HFD containing 60% calories from fat, 20% from carbohydrates, and 20% from protein for 15 wk time period. Six additional mice (control group) were fed for the same time (15 wk) with low fat diet (LFD) containing 10% calories from fat, 70% from carboydrates, and 20% from protein. Intraperitoneal insulin tolerance test (IITT) was performed following previously described procedures[5,22], using human insulin (Human Actrapid, Novo Nordisk), 0.25 U/kg body weight, then measuring blood glucose levels at 0, 15, 30, 45, 60 min after insulin injection. At the end of 15 wk, mice were euthanized by cervical dislocation, epididimal WAT tissue rapidly removed and frozen in liquid nitrogen *until* analysis.

All animal procedures were performed according to the guidelines of the Charité universitätsmedizin Berlin and were approved by the Landsamt für Gesundheit und Soziales (Berlin, Germany) for the use of laboratory animals and according to the current version of the German Law on protection of animals for scientific purposes.

Statistical analysis

All calculations were analyzed with GraphPad Prism Software. Mean values were compared with *t*-test. A P value < 0.05 (two tailed) was considered significant.

RESULTS

MMP-11 expression in 3T3-L1 cells

We first examined the expression of *MMP-11* during 3T3-L1 adipogenesis. Total RNA was prepared at different stage of adipocyte cell differentiation and *MMP-11* mRNA expression levels were measured. As shown in Figure 1, *MMP-11* mRNA abundance was low in 3T3-L1 pre-adipocytes, increased in confluent culture cells, reaching maximum expression in mature 3T3-L1 adipocytes (Figure 1).

MMP-11 expression in in vitro insulin resistance

To induce insulin resistance *in vitro*, fully differentiated 3T3-L1 adipocytes were treated with TNF-α (2.5 nmol/L) and at the same time incubated in hypoxia (1% O_2) for 24 h. Then, *MMP-11* mRNA and protein expression levels were measured. As shown in Figure 2A, a clear increase in both mRNA and protein expression of the *MMP-11* proteinase was observed in insulin resistant 3T3-L1 cells, as compared to normal, non-insulin

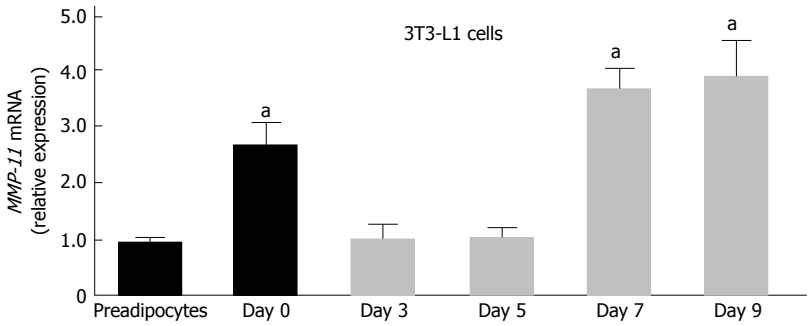

Figure 1 Expression of *matrix metalloproteinase-11* during adipocyte differentiation in 3T3-L1 cells. Total RNA was extracted from 3T3-L1 cells at preadipocyte and confluent (day 0) stages, and after induction of differentiation (days 3, 5, 7 and 9). *MMP-11* mRNA expression was measured by RT-PCR. Results are the means ± SE of three independent experiments, each performed in triplicate. [a]*P* < 0.05 *vs* undifferentiated preadipocytes. *MMP-11*: *Matrix metalloproteinase-11*.

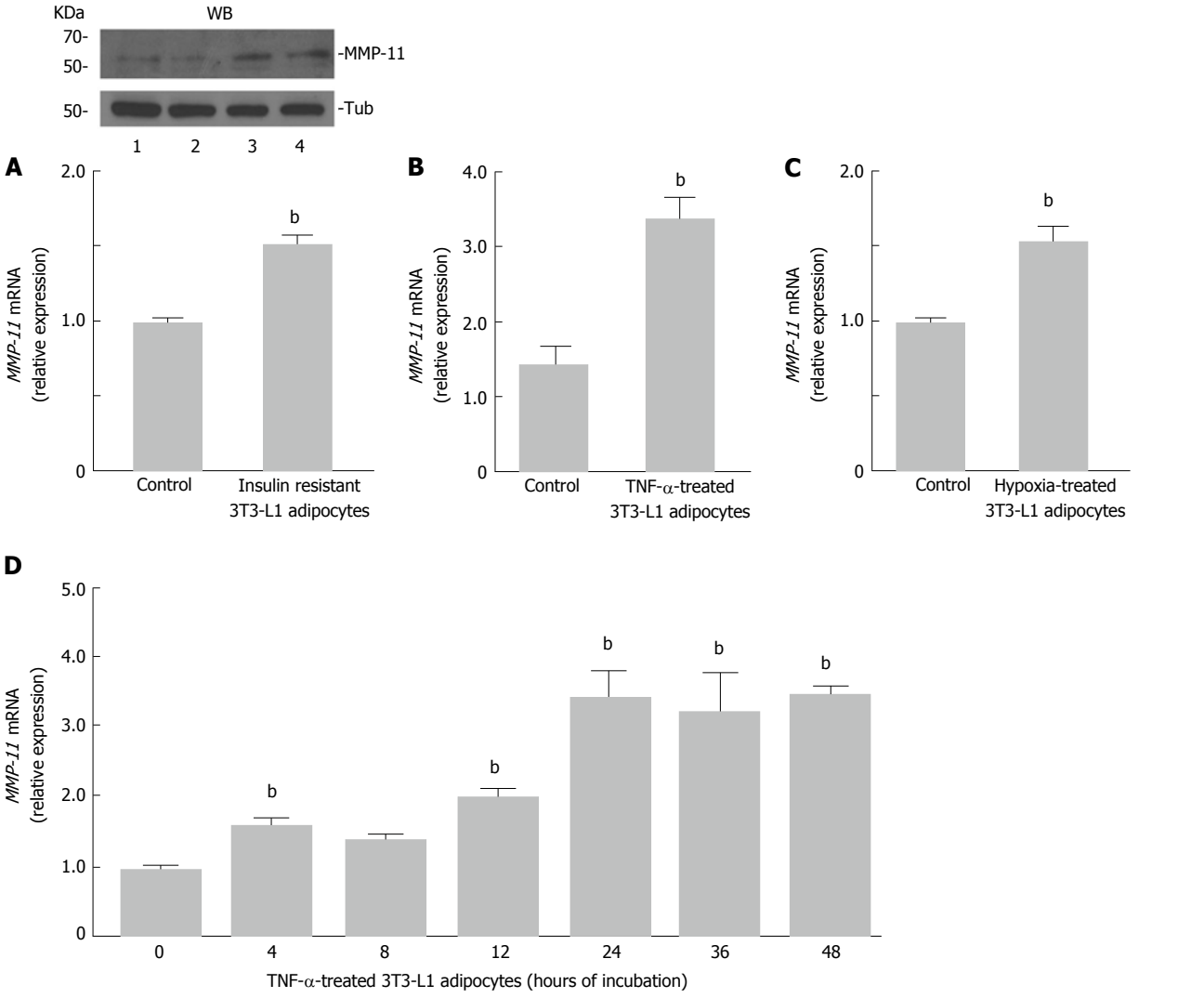

Figure 2 *Matrix metalloproteinase-11* expression in insulin-resistant 3T3-L1 adipocytes. A: Fully differentiated 3T3-L1 adipocytes were co-treated with TNF-α (2.5 nmol/L) and hpoxia (O_2 1%) for 24 h, and *MMP-11* mRNA was measure by RT-PCR. Results are the means ± SE of three independent experiments, each in triplicate. [b]*P* < 0.01 *vs* untreated (control) cells. A representative western blot (WB) of *MMP-11* is shown for each experimental condition. Lanes: 1 and 2, *MMP-11* protein expression in untreated 3T3-L1 cells (control); 3 and 4, *MMP-11* protein expression in insulin-resistant 3T3-L1 cells. Tubulin (Tub), control of protein loading; B: 3T3-L1 adipocytes were treated with TNF-α alone, at a final concentration of 2.5 nmol/L, and *MMP-11* mRNA levels were measured 24 h later by RT-PCR. Results are the means ± SE from three independent experiments. [b]*P* < 0.01 *vs* untreated control cells; C: 3T3-L1 adipocytes were incubated in normoxic (control) or hypoxic condition (O_2 1%) for 24 h, total RNA was extracted and the expression of *MMP-11* was determined by RT-PCR. Results are the means ± SE from three independent experiments in triplicate. [b]*P* < 0.01 *vs* control; D: Time-course of *MMP-11* mRNA expression in differentiated 3T3-L1 adipocytes, in the presence of TNF-α (2.5 nmol/L) alone. *MMP-11* mRNA was measured by RT-PCR at the indicated time points, after TNF-α treatment. Results are the means ± SE from three independent experiments, each in triplicate. [b]*P* < 0.01 *vs* time 0. *MMP-11*: *Matrix metalloproteinase-11*.

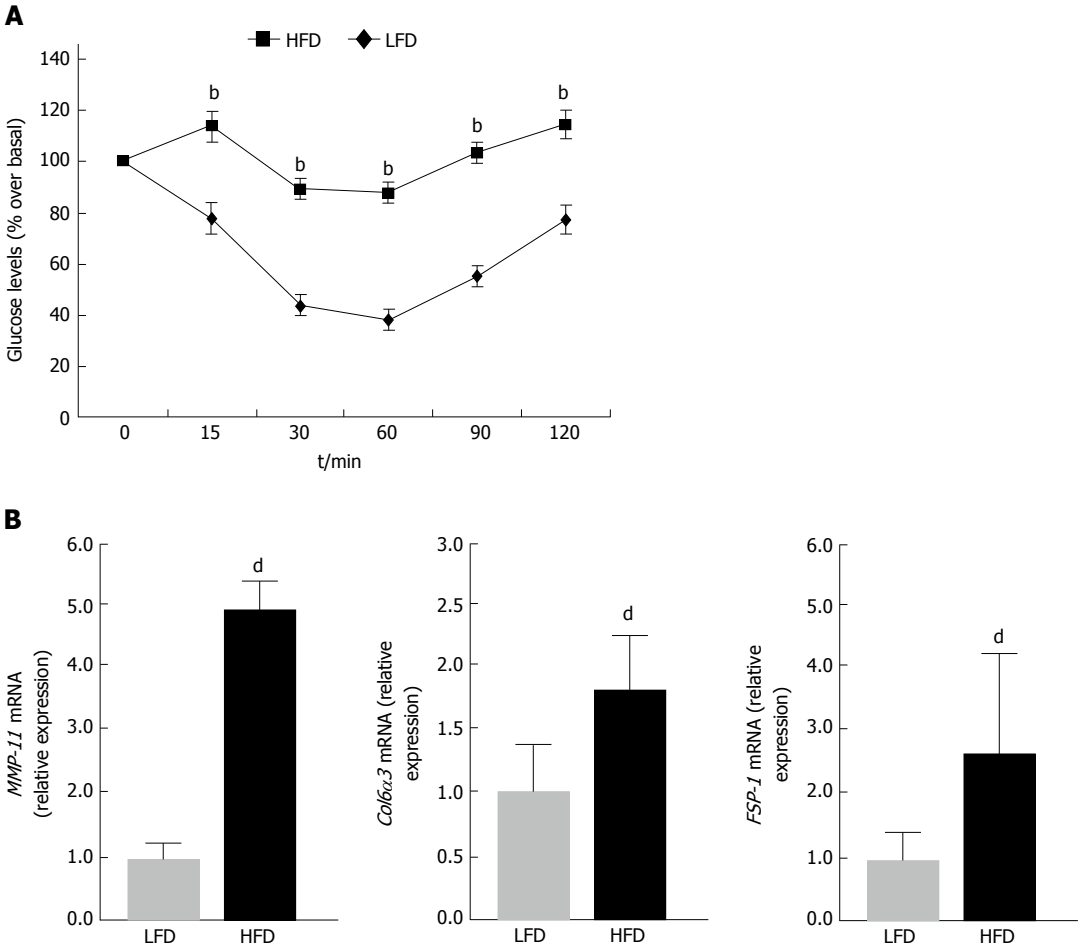

Figure 3 Intraperitoneal insulin tolerance test and the expression of *matrix metalloproteinase-11*, collagen type Ⅵ alpha 3 and fibroblast-specific protein 1 in mice under different dietary conditions. A: IITT. Insulin tolerance was assessed in 12 h fasted mice, intraperitoneally injected with insulin (0.25 U/kg body weight). LFD (n = 6); HFD (n = 10). $^{b}P < 0.01$ *vs* LFD; B: MMP-11, *Col6α3* and *FSP-1* mRNA expression in WAT of mice fed a low-fat (LFD) or high-fat (HFD) diet (n = 6 per each group). Results are the means ± SE of three independent measurements from each animal. $^{d}P < 0.001$ *vs* LFD, for each group. MMP-11: *Matrix metalloproteinase-11;* IITT: Intraperitoneal insulin tolerance test; *Col6α3*: Collagen type Ⅵ alpha 3; *FSP-1*: Fibroblast-specific protein 1.

resistant 3T3-L1 adipocytes. To better understand the effect of each treatment on *MMP-11* expression, we carried out separate experiments in which *MMP-11* mRNA levels were measured in fully differentiated 3T3-L1 adipocytes treated with either 2.5 nmol/L of TNF-α for 24 h, or subjected to 24 h hypoxia alone. As shown in Figure 2B, *MMP-11* mRNA abundance was approximately four-fold higher in TNF-α treated cells compared to untreated 3T3-L1 adipocytes, thereby indicating that upregulation of *MMP-11* expression can be at least in part regulated by the pro-inflammatory TNF-α molecule. On the other hand, hypoxia alone induced a slight but significant increase of *MMP-11* mRNA expression compared to normoxia (Figure 2C). A time-course study of *MMP-11* mRNA expression, using TNF-α alone over a 48 h period, showed that *MMP-11* mRNA levels were significantly increased already after 4 h and this increase was maintained thereafter, reaching a plateau level at 24 h of exposure (Figure 2D).

MMP-11 expression in in vivo insulin resistance

In attempt to validate the results obtained *in vitro*, in insulin-resistant *3T3-L1* adipocytes, mRNA expression studies were carried out also *in vivo*, in a mouse model of insulin resistance[23,24]. To this end, ten male mice were fed with HFD for 15 wk, whereas six other mice, which were used as controls, were subjected to normal chow diet, for the same time period. At the end of the diet treatment, mice fed with HFD were obese relative to control mice (43.6 ± 2.1 g *vs* 27.5 ± 1.7 g, respectively; P < 170829E-06), and developed insulin resistance as assessed by IITT (Figure 3A). Gene expression analysis to evaluate the levels of *MMP-11* was then performed in both groups of mice. As shown in Figure 3B, *MMP-11* mRNA was significantly higher in WAT from diet-induced obese mice than in WAT from lean mice, indicating that hyperexpression of *MMP-11* may also occur *in vivo*, in the whole animal, after induction of an insulin-resistant state, thereby suggesting that abnormal activation of *MMP-11* may have direct consequences on the molecular mechanism(s) related to adipocyte dysfunction. In this regard, the expression profile of two major fibrosis marker genes, collagen type Ⅵ alpha 3 (*Col6α3*) and fibroblast-specific protein 1 (*FSP-1*), was also measured in parallel experiments. As shown in Figure 3C, both these markers were significantly upregulated in WAT from obese mice compared to lean animals (Figure 3C), highlighting the possibility, in our

obese mouse model, for an ECM dysregulation that would support the hypothesis that this ECM remodeling could indeed exert an adverse effect on adipocyte functions.

DISCUSSION

Adipose tissue is surrounded by ECM elements that provide the right support for adipocyte cell growth and expansion, and maintenance of adipocyte specific functions. Alterations in the organization and flexibility of the ECM as a cause of adipose tissue dysfunction have been reported[25], together with the observation that several MMPs could be involved in these adverse events[26].

In the present work, we focused our attention on the *MMP-11* and its activation in conditions of insulin resistance, either *in vitro*, in 3T3-L1 mouse adipocytes, or *in vivo*, in obese mice. For the first time, in the present study, we show that *MMP-11* was upregulated both in insulin resistant cells treated with TNF-α and/or hypoxia (two elements frequently associated with obesity), and in adipose tissues from insulin-resistant obese mice, suggesting that a direct link may exist between activation of *MMP-11* and adipocyte cell dysfunction. Our data are consistent with previous observations that adipokines and hypoxia can alter the expression of MMPs. In this regard, it has been shown that TNF-α upregulated MMP-9 expression in the osteoblast-like MC3T3-E1 cell line[27], while in another study it was found that MMP-2 expression increased in response to hypoxia[28]. Furthermore, an involvement of both MMP-2 and *MMP-11* in ECM degradation and collagen accumulation, associated with adipocyte dysfunction, was reported previously[29]. It can be hypothesized that upregulation of *MMP-11* in insulin resistance may reflect the increase of nuclear proinflammatory transcription factor(s) whose effective role needs to be investigated.

Fibrosis is considered a new hallmark of the pathological dysfunction of WAT[25]. In our study, it is also interesting to note the alteration in the expression of genes related to fibrosis (*Col6α3* and *FSP-1*) in WAT from nutritionally induced obese mice. A link between *Col6α3* and *MMP-11* has been reported before[29]. Thus, our data in this context well support previous reports that overexpression of MMPs, *via* degradation of ECM, could be implicated in adipose tissue remodeling[25], and this can play a role in the pathological dysfunction of adipose tissue, which leads to insulin resistance.

Our results appear to challenge findings obtained by studying the *MMP-11* knock-in transgenic mouse[30], in which protection from diet-induced obesity was reported, together with a condition of enhanced glucose tolerance and insulin sensitivity due to increased IGF-I bioactivity[30]. The explanation for these divergent results may reside in the fact that overexpression of active *MMP-11* in the skin of the transgenic animal may not necessarily reflect the situation *in vitro*, in 3T3-L1 adipocytes and *in vivo*, in WAT from diet-induced obese mice. On the other hand, the existence of compensatory mechanisms/changes that may contribute to counteract genetic manipulation has been proposed[31-35].

Overall, although further studies are still necessary to clarify the role of *MMP-11* in insulin resistance, we believe our findings may contribute to shed light on the early process of adipose tissue dysfunction commonly associated with obesity and obesity-related insulin resistance.

COMMENTS

Background

Insulin resistance is a common metabolic disorder, in which peripheral target tissues fail to respond adequately to insulin, thereby predisposing to type 2 diabetes and other dysmetabolic conditions. More recent discoveries have now strengthened the hypothesis that adipose tissue dysfunction could be the primum movens in the development of insulin resistance. Therefore, studies have been focused on exploring the molecular mechanism(s) underlying adipocyte dysfunction.

Research frontiers

Matrix metalloproteinases (MMPs) are a class of endopeptidases that contribute to the degradation of the extracellular matrix components. It has been discovered that they are involved in adipogenesis and remodelling of adipose tissue. A better understanding of the role and function of MMPs in adipose tissue will open new frontiers of investigations.

Innovations and breakthroughs

For the first time, the authors demonstrate that overexpression of *MMP-11* occurs in *in vitro* and *in vivo* models of insulin resistance.

Applications

This study suggests that *MMP-11* could be involved in the early stage of obesity-related insulin resistance. Thus, as a secreted serum protein, *MMP-11* could serve as an early biomarker of adipose tissue dysfunction. Research in this area will lead to advancement in understanding the pathophysiology of insulin resistance, as well as advancement in drug development and therapy.

Peer-review

The paper is straight forward, well written, and it adds novel information on the topic.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical profile of diabetes at diagnosis among children and adolescents at an endocrine clinic in Ghana

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Abstract

AIM

To determine the clinical features of diabetes in children and adolescents in Ghana.

METHODS

Retrospective review of clinical features of all children and adolescents with new-onset diabetes seen at the paediatric endocrinology clinic of Komfo Anokye Teaching Hospital in Kumasi, from February 2012 to Auguest 2016.

RESULTS

One hundred and six subjects presented with diabetes. Ninety (84.9%) were diagnosed by clinical features and family history as type 1, and 16 (15.1%) type 2. For type 1 subjects, age range at diagnosis was 0.9-19.9 year (y), peak age of onset 12-13 year, and 3.3% were < 5 year, 21.1% 5- < 10 year, 45.6% 10- < 15 year and 30.0% 15- < 20 year. Seventy-one point one percent were female. Common clinical features were polyuria (100%), polydipsia (98.9%), and weight loss (82.2%). Mean BMI SD was -0.54, range -3.84 to 2.47. 60.0% presented in diabetic ketoacidosis (DKA). Nine had infections at onset (skin, abscess, leg ulcer). Mean

± SD HbA1c at diagnosis was 12.7% ± 1.9% (115 ± 21 mmol/mol). Four have since died: Hypoglycaemia (2), recurrent DKA (1), osteosarcoma (1). Two other type 1 cases died of DKA at presentation in emergency before being seen by the paediatric endocrinologist. Crude mortality rate including these 2 cases was 32.2/1000 patient years. Type 2 cases were 81% female, age of onset 9-19 year. Mean BMI SD was 1.49, range -0.87 to 2.61. Forty-three point eight percent presented in DKA. All type 2 cases had acanthosis nigricans. Overall, 9.8% did not have home refrigeration, most using clay pot evaporative cooling for insulin storage.

CONCLUSION

Type 1 occurs with a female preponderance and high DKA rates. Type 2 also occurs. Typology based on clinical features is difficult. Community and professional awareness is warranted.

Key words: Children; Diabetes; Developing countries; Ghana; Mortality

Core tip: In this study of 106 consecutive new diagnoses of diabetes in young people < 20 years in a tertiary referral centre in Ghana, type 1 predominated (85%) with the remaining cases clinically diagnosed as type 2. Both types had a female preponderance. Type 1 peak age of onset was 12-13 years. All type 2 subjects had acanthosis nigricans. Most presented in ketoacidosis signifying a lack of awareness of presentation features. Clinic numbers quickly rose due to availability of supplies and expertise. Further typology studies are indicated to further define diabetes type.

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INTRODUCTION

Understanding the presentation and types of diabetes in children and youth in any particular country is essential in improving awareness and care. Ghana is a less-resourced country in West Africa. There is no published data on clinical features of young Ghanaians with diabetes and, as with many low-income countries[1], there is little public health sector support and also lack of awareness amongst both health workers and the general society[2]. Insulin is only intermittently available from the government health service, and blood glucose meters and strips and HbA1c testing are not provided by the Ghana National Health Insurance Scheme. The families must often buy these supplies, often at premium prices[3], which many cannot afford to do[2].

The lack of awareness leads to misdiagnosis and mismanagement. Ketoacidosis is very common at initial presentation in Africa[2,4-6], and can mimic infections and acute medical conditions[7-10].

This study determined the clinical features of children and adolescents presenting with diabetes at the Paediatric Endocrine Clinic, Komfo Anokye Teaching Hospital (KATH) at Kumasi, a tertiary referral centre for northern Ghana. This clinic has been supported since 2012 by the International Diabetes Federation (IDF) Life for a Child Program[11] with provision of insulin, blood glucose meters and strips, insulin syringes, HbA1c testing, education materials, and mentoring.

MATERIALS AND METHODS

Study subjects

A total of 106 subjects were enrolled, all < 20 years of age at diagnosis. They included all subjects being followed at the Paediatric Endocrine Clinic on 24/02/2012 as well as all new diagnoses until 31/08/2016. During this period, two other subjects < 20 years old (both female, aged 12 and 15 years old respectively) presented with diabetic ketoacidosis (DKA) and died in the emergency department. They were not seen by the pediatric endocrinologist or in the clinic, and no further information is available. Therefore, they were included in the mortality rate calculation, but excluded from the remainder of the analysis. The study was approved by the institutional ethics board and subjects gave informed consent.

Demographic data

Date of birth and sex was recorded, as well as date of diagnosis.

Clinical parameters

Diabetes was diagnosed according to standard World Health Organization criteria[12]. Determination of the type of diabetes was made by the local investigators according to available clinical features and history. Type 1 patients generally had lower body mass index (BMI), more rapid symptom onset, and were more sensitive to insulin. Type 2 patients had higher BMI, acanthosis nigricans, and needed more insulin with time, with insulin requirements falling sharply in those started on metformin. The presence of polyuria, polydipsia, weight loss, malnutrition and ketoacidosis at the time of diagnosis were recorded. Body weight and height were measured by electronic scales and stadiometer respectively with subjects wearing light-weight clothing and without shoes. BMI was then calculated. BMI SD scores were calculated using World Health Organization standards[13,14].

Ketoacidosis was defined by clinical features along

with an elevated blood glucose and ketonuria (blood gas measurements are generally not available). Family history of type 1 diabetes, and history of other medical conditions were also recorded.

Biochemical parameters

Blood glucose was measured in a laboratory *via* venous sample. HbA1c was measured using a Clover analyzer (Infopia, Anyang, South Korea).

Socioeconomic parameters

The following information was collected for each subject: Whether the mother or father was living with the subject, mother's and father's educational level, who was the primary caregiver, whether the primary caregiver was literate, time spent travelling to clinic, and average weekly household income. It was also recorded whether the subject was at school, whether diabetes was limiting school attendance, and whether they were in the appropriate grade for age, and how well overall the young person was psychologically coping with their diabetes (rated as poor, average or good). Finally, the method of insulin storage was recorded.

Crude mortality rate was calculated as the total number of deaths divided by the sum of the periods from the commencement of the study, or from the date of diagnosis if they were diagnosed after the study commenced. It is expressed as mortality per 1000 patient years.

Statistical analysis

Data and descriptive statistics were managed in Excel. Unpaired *t*-test and χ^2 tests were done using the Social Science Statistics on-line calculators[14]. Significance was set as < 0.05.

RESULTS

One hundred and six subjects with diabetes were seen at the paediatric endocrine clinic. Ninety (84.9%) were diagnosed by clinical features and family history as type 1, and 16 (15.1%) type 2.

Type 1 subjects

Table 1 shows age of onset and gender of the 90 type 1 subjects, as well as BMI, BMI SD score, presence of DKA at diagnosis, and blood glucose and HbA1c at diagnosis. Figure 1A shows the distribution of age of onset. Three point three percent were < 5 years, 21.1% 5- < 10 years, 45.6% 10- < 15 years and 30.0% 15- < 20 years. Common clinical features at diagnosis were polyuria (100.0%), polydipsia (98.9%), and weight loss (82.2%). Nine (10%) had infections at onset (tinea capitis, abscess, leg ulcer, vaginal candidiasis).

Nine type 1 subjects had a first-degree relative with type 1: Sister (two subjects), brother (three), sister and brother (two), two brothers (one), mother (one), with one other subject having a grandmother with type 1. The number of insulin injections each day was two for 17 (18.9%) subjects, three for 24 (26.7%), five for 47 (52.2%) and unknown for two (2.2%). The type of insulin was pre-mixed for 11 (12.2%) subjects, and short-acting combined with long-acting for 79 (87.8%).

Four of the 106 patients have since died: One from metastatic osteosarcoma (diagnosed well after onset of type 1), two from hypoglycemia at home (2 years after diagnosis), and one from a recurrent episode of DKA (2 years after diagnosis). Two others died in emergency department during treatment of DKA at diagnosis, and were not seen by the paediatric endocrinologist (see Methods). Crude mortality rate for the type 1 patients was six deaths per 186 patient years (*i.e.*, 32.2 deaths per 1000 patient years).

Type 2 subjects

For the 16 type 2 cases, Table 1 shows age of onset and gender, as well as BMI, BMI SD score, presence of DKA at diagnosis and blood glucose and HbA1c at diagnosis. Figure 1B shows age of onset. Six point three percent were 5- < 10 years, 68.7% 10- < 15 years and 25.0% 15- < 20 years. Common clinical features at diagnosis were polyuria (100.0%), polydipsia (100.0%), and weight loss (93.8%). All type 2 subjects had acanthosis nigricans. None had infections at onset. One had substantial visual loss at diagnosis, of uncertain aetiology. Three subjects had first degree relatives with type 2, and two others had a second-degree relative. Four subjects (25.0%) were treated with metformin only, six (37.5%) with insulin only, five (31.3%) with metformin together with insulin and one (6.3%) also with glibenclamide. No subject with type 2 died.

Increase in clinic numbers

Figure 2 shows the rapid increase in clinic numbers in the 4 years from June 2012 to June 2016 - clinic numbers were censused at the end of every half-year.

Socioeconomic factors

The mother was living with the subject in 83 (78.3%) cases and the father in 78 (73.6%). The mother's educational level was primary school in 31 (29.2%) cases, high school in 26 (24.5%), tertiary in 10 (9.4%), no schooling in 38 (35.8%) and unknown in 1 (0.9%). The father's educational level was primary school in 26 (24.5%) cases, high school in 31 (29.2%), tertiary in 23 (21.7%), no schooling in 21 (19.8%) and unknown in 5 (4.7%). The primary caregiver was the mother in 75 (70.8%) cases, father in 15 (14.2%), sister in 3 (2.8%), brother in 2 (1.9%), grandmother in 4 (3.8%), aunt in 6 (5.7%) and self in 1 (0.9%). The primary caregiver was literate in 79 (74.5%) cases. Twenty-four (22.6%) families had to travel long distances (> 2 h travelling time each way) for supplies and review. The average weekly household income was 63 USD and the range was 5-625 USD. Ninety-six (90.6%) subjects were attending school. Diabetes was limiting attendance at

Table 1 Characteristics of type 1 and type 2 subjects at diagnosis

	Type 1	Type 2	Difference
Number (%)	90 (84.9)	16 (15.1)	$P < 0.001$
Male: Female ratio	1:2.5	1:4.3	Not significant
Age at diagnosis (range), yr	0.9-19.9	9.0-18.7	-
Age at diagnosis (mean ± SD), yr	12.6 ± 3.8	13.6 ± 2.3	Not significant
Peak age at diagnosis, yr	12-13	13-14	-
Diabetic ketoacidosis at onset (%)	54 (60.0)	7 (43.8)	Not significant
BMI at onset (mean; range)	18.1; 12.5-34.7	27.8; 17.6-38.2	-
BMI SD score at onset (mean; range)	-0.54, -3.84-2.47	1.49, -0.87-2.61	$P < 0.001$
HbA1c at diagnosis (mean ± SD) (%) (mmol/mol)	12.7 ± 1.9 (115 ± 21)	12.8 ± 1.5 (116 ± 16)	Not significant

BMI: Body mass index; HbA1c: Glycosylated haemoglobin.

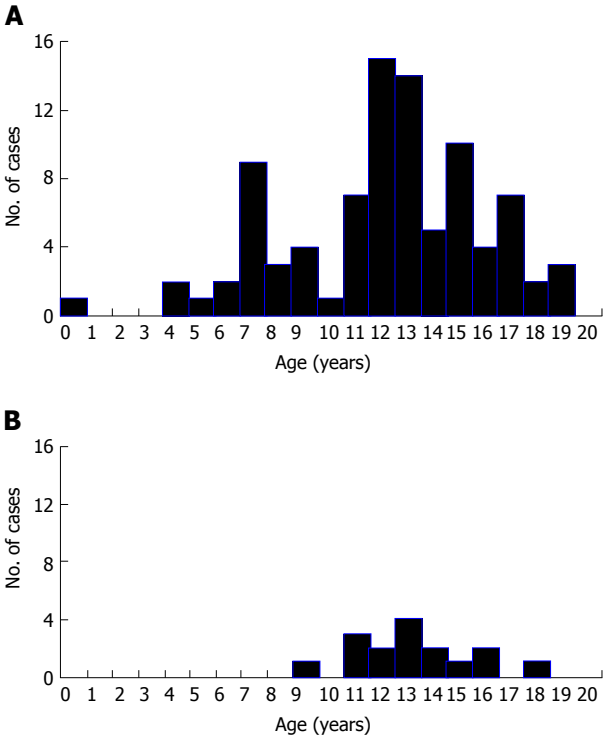

Figure 1 Age at diagnosis of subjects < 20 years of age with diabetes in Kumasi, Ghana. A: Type 1 diabetes: Age at diagnosis; B: Type 2 diabetes: Age at diagnosis.

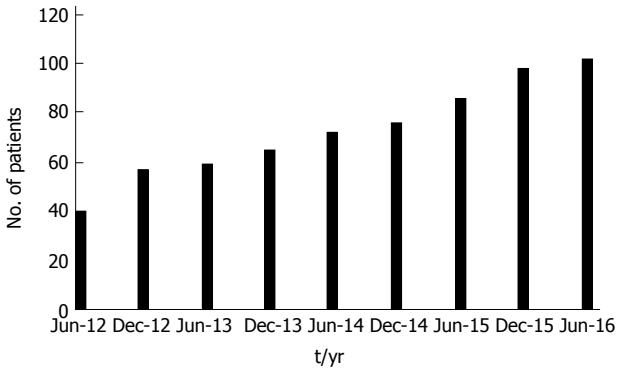

Figure 2 Numbers of patients with diabetes being seen at the paediatric endocrine clinic in Kumasi, Ghana.

school for 44 (45.8%) subjects, not limiting attendance for 51 (53.1%) and unknown for 1 (1.0%). In addition, 18 (18.8%) were not in the appropriate grade for their age, 76 (79.2%) were in the appropriate grade, and 2 (2.1%) unknown. Diabetes coping abilities were assessed as poor for 12 (11.3%) subjects, average for 37 (34.9%), good for 55 (51.9%) and unknown for 2 (1.9%). Ninety-five (89.6%) subjects were literate or learning at school, 8 (7.5%) were not literate and 3 (2.8%) unknown. Insulin storage method was a refrigerator at the family home for 92 subjects (90.2%), for two a refrigerator outside the home (2.0%) and for eight clay pot evaporative cooling (7.8%).

DISCUSSION

There are very limited published data on diabetes in young people in Ghana. The International Diabetes Federation Diabetes Atlas estimates an incidence of type 1 diabetes of 2.9 per 100000 children < 15 years per annum and a prevalence of 18.0 per 100000 children < 15 years: An estimated 1800 children in the country[15,16]. This is however based on a small study in Nigeria in 1992[17]. It is possible that the current Ghanaian incidence is different from this estimate, and the prevalence/incidence ratio is likely to be substantially lower as the Atlas estimates do not assume any mortality[16]. In Ghana, it is likely that many children and young adults with diabetes die before they are diagnosed, or die during the first episode of DKA or early in ongoing management. DKA is frequently misdiagnosed at first as another condition - with a legion of alternatives including pneumonia, gastroenteritis, malaria, typhoid, appendicitis and a number of other conditions[1,7-10]. At a training workshop organised by Ghana Society of Pediatric Endocrinology and Diabetes (GSPED) in August 2016, some participants from district and regional hospitals admitted that most of their patients with DKA die. Indeed, two centres admitted that all such patients have died during management. The rate of DKA at onset in type 1 subjects was high at 60.0%, consistent with rates of 69.8% reported from South Africa[4], 75% from Tanzania[5], and 77.1% from Nigeria[6]. Community and health professional awareness on the presentation of diabetes in young people is warranted given this late presentation and the likely substantial numbers of

deaths where the correct diagnosis is not made at all. Type 1 patients were generally lean or underweight at diagnosis, and presented with classic symptoms. There was a female preponderance as is often observed in low-incidence countries[18].

There was also a female preponderance in the type 2 population, consistent with data in adults in Kumasi[19]. Type 2 subjects were often overweight. This is of concern, as overweight is now not uncommon in Ghanaian children and youth[20,21]. All had acanthosis nigricans - a physical marker suggestive of insulin resistance[22]. Interestingly, seven of 16 type 2 subjects presented in DKA, suggesting a diagnosis of ketosis-prone type 2 diabetes, which is well-reported in populations in Africa and of African descent[23,24].

The youngest child was 10 mo of age at diagnosis. Development of diabetes at a young age can indicate a monogenic cause, and genetic testing is indicated if the onset is < 6 mo of age or if there are syndromal features of known single-gene defects (which were not present in the infant in this series)[25]. In some of these cases, alternate non-insulin therapy may be possible[25].

Even with accurate diagnosis, mortality has been high in studies in sub-Saharan Africa[26-28], but there are indications it is falling - for instance in Rwanda it was found to be between 13.9-40.2 per 1000 patient years, depending on the fate of those lost to follow-up[29]. The figure of 32/1000 from this study is in this range - and in Rwanda like in Ghana, care is improving as supplies are made available[30]. This improvement in survival is seen in the dramatic increase in the clinic population from 23 to 102 cases over the five years - "if you build it they will come" - and not just come but survive and thrive. Such rapid increases in numbers in clinics that are able to provide standard care (also seen in Tanzania[31]) indicate the strain that will be on resources as survival improves as insulin and other critical supplies are provided by programs such as IDF Life for a Child, and paediatric endocrinologists, trained in Kenya[32] and elsewhere, return to their home countries to establish clinics.

Patient education is critical in improving care. At this study clinic, all patients are called on the telephone to come in for education every fortnight. They are taught at an appropriate educational level about the pathophysiology of diabetes, how to appropriately store and administer insulin, injection sites, adjust doses, manage diet and exercise, detect acute complications, *etc*.

The study results demonstrate the socio-economic challenges faced by many subjects, and the necessity for support with supplies, consistent with past reports[1-3,28]. A number of young people were also facing challenges with continuing their education, as demonstrated in the study by Kratzer[2].

Some families do not have access to home refrigeration for insulin storage, and so place the insulin in a clay pot using evaporative cooling. Such methods do substantially reduce storage temperatures unless humidity is very high[33].

Limitations

The major limitation of this study is the lack of ability and resources to measure autoantibodies and C-peptide to confirm the diagnosis of type 1 or type 2, or an atypical form. Such assistance with typology would not only be interesting scientifically, but would be helpful to individualise management. However, the presence or absence of autoantibodies alone may not be categorical in this population. Agyei-Frempong *et al*[34] in a study of autoimmunity in a population of adults with diabetes in Kumasi found that glutamic acid decarboxylase (GAD) antibody and/or insulinoma antibody (IA2) were present in 35% of those on insulin and 16.5% of those not requiring insulin.

Summary and recommendations

In summary, both type 1 and type 2 diabetes occur in young people in northern Ghana, with high rates of DKA at onset, and a female preponderance. Deaths in the first few years are still not uncommon. Community and health professional awareness is indicated to achieve prompt and accurate diagnosis and prevent deaths at onset. Although not assessed in this study, it is reasonable to conclude that further health professional and patient education is needed to continue to improve management, and therefore reduce the risk of long-term complications. Improvements in the availability of diagnostic technology (particularly blood glucose meters and strips) is also indicated. A patient support group would also be very beneficial.

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COMMENTS

Background

Limited information is available on types of diabetes in young people in Africa, nor on prognosis.

Research frontiers

The epidemiology and prognosis of diabetes in young people in sub-Saharan Africa is of importance as services are developed to look after these young people.

Innovations and breakthroughs

This study shows that both type 1 and type 2 diabetes are occurring in young people in Ghana, with some phenotypic overlap. Mortality was found to be 32.2 per 1000 patient years.

Applications

The study shows how numbers of children and young people in a clinic in a less-resourced country quickly grow as care is given in a paediatric endocrine clinic.

Peer-review

This study offers a valuable insight in the clinical profile of diabetes in population of children and adolescents in Ghana. The subject is interesting and worth investigating, since the data regarding diabetes burden in Africa are still scarce and the study population is particularly vulnerable.

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ORIGINAL ARTICLE

Retrospective Study

Eye and foot checks in patients with diabetes on haemodialysis: Are they done, and who does them?

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Abstract

AIM

To determine if retinal and foot checks are carried out on patients with diabetes receiving haemodialysis.

METHODS

Eighty-four patients with diabetes receiving haemodialysis were asked if they recalled having eye and foot screening in the last year, and if so, by whom was the check done.

RESULTS

Seventy-seven (91.7%) patients recalled having an eye check in the preceding 12 mo. Of these, 52 (67.5%) did so in an ophthalmology clinic, 17 (22%) in retinal screening, three (3.9%) in an optician clinic. Three patients (3.9%) went to both ophthalmology and retinal screening, and two (2.6%) attended an ophthalmology and optician. Seventy (83.3%) patients recalled having a foot check in the preceding 12 mo. Of these, 33 (47.1%) were done by practice nurse, 14 (20%) by a diabetes nurse, 11 (15.7%) by a general practitioner, eight (11.4%) by a chiropodist, and four (5.7%) were each checked by renal nurse, diabetes consultant, junior doctor, or unknown person at a foot clinic.

CONCLUSION

Most patients with diabetes on haemodialysis are able to recall having an eye check in the last year, although 8.3% could not. A significant proportion of patients could not recall having a foot check (16.7%) in the last year. This baseline audit suggests that an improvement in the rate of foot screening is important to achieve in patients with diabetes on haemodialysis in our unit.

Key words: Diabetes; Haemodialysis; Foot screening; Retinal screening

Core tip: Diabetes is the commonest cause of end stage renal failure in many countries. Patients with diabetes on haemodialysis are at high risk of retinal and foot problems, and need regular screening to ensure they do not develop problems related to these complications. Our survey suggests that most patients are getting eye checks, but a significant number are not getting foot checks. This is an important area for all dialysis units to consider. We recommend that patients have foot screening whilst on dialysis, which may require further training for dialysis nurses.

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INTRODUCTION

Diabetic nephropathy is the leading cause of end-stage renal failure in the United Kingdom[1]. Screening programmes enable detection of early changes associated with microvascular complications of diabetes, including diabetic retinopathy and peripheral neuropathy. Many national guidelines recommend that all patients with diabetes have yearly screening of feet and eyes to reduce the risk of blindness and avoidable limb amputations[2,3]. With the increasing prevalence of diabetes, attendance at screening programmes is of the utmost importance in order to reduce the risk of complications.

Patients with diabetes who have end stage renal failure (ESRF) on regular haemodialysis attend hospital for dialysis very frequently, and as a result find it difficult to attend other appointments. We have previously noted poor attendance to other clinics and appointments in patients on haemodialysis. East London is an area of high social deprivation, and many patients are elderly, with multiple co-morbidities, whose first language is often not English, and these factors may affect their ability to access healthcare[4]. Patients with diabetes on haemodialysis are at particular risk of foot and eye problems[5]. Microvascular complications of diabetes arise due to poor glycaemic control, and indeed haemodialysis patients with poor glycaemic control have been found to have poorer survival compared to those with good glycaemic control[6].

Recent United Kingdom guidelines highlight the need for annual foot and eye screening for patients with diabetes on haemodialysis[4]. The aim of this study was to determine if patients with diabetes on our haemodialysis unit could recall having retinal screening and foot surveillance in the past year, and to find out who had performed this.

MATERIALS AND METHODS

This retrospective study was carried out on the dialysis unit of the Royal London Hospital, a tertiary centre which serves a large cohort of renal patients in East London, United Kingdom. A brief questionnaire was designed for patients with diabetes receiving dialysis, asking whether patients recalled having "a diabetes eye check" or "diabetes foot check" in the past 12 mo. Patients who had received a diabetes eye check were asked where this had taken place: At an optician, eye clinic, retinal screening service or elsewhere. Patients who had a diabetes foot check where asked who had performed the procedure; a doctor, diabetes nurse, renal nurse or podiatrist.

Participants were recruited to the study from August to September 2015, whilst receiving haemodialysis on the renal unit. Inclusion criteria for the study included: Patient currently receiving haemodialysis, patient was diagnosed with diabetes for at least a year and able to receive care in the community. Patients were excluded from the study if they had communication difficulties.

All statistical analysis and graphs were performed using GraphPad Prism 7 (GraphPad software inc, California, United States) software. Quantitative data were expressed as frequencies or mean ± SD as appropriate. Qualitative data were expressed as frequencies.

RESULTS

Patient characteristics

Eighty-four patients met the inclusion criteria and agreed to participate in the study. Patient characteristics are shown in Table 1. Sixty point seven percent of the participants were male and 39.3% were female. The mean age of the cohort was 63.9 ± 10.35 years. Insulin only therapy was used by 53.6% of the participants. The remaining participants were diet-controlled (11.9%), on medication only (19%) or medication and insulin (15.5%).

Eye checks

Figure 1 shows eye check uptake in the patients

Table 1 Demographic characteristics of patients surveyed *n* (%)

Variables	Patients
Gender	
Male	51 (60.7)
Female	33 (39.3)
Age (mean ± SD)	63.9 ± 10.35
Ethnicity	
African - Caribbean	38 (45.2)
Asian - Bangladeshi	22 (26.2)
Asian - Indian	4 (4.8)
Asian - Pakistani	2 (2.4)
Asian - Other	4 (4.8)
White - British	9 (10.7)
White - Other	2 (2.4)
Other	3 (3.6)
Treatment regimen	
Diet only treated	10 (11.9)
Oral hypoglycaemic only treated	16 (19.0)
Insulin + oral hypoglycaemic treated	13 (15.5)
Insulin only treated	45 (53.6)

surveyed. Seventy-seven (91.7%) of patients reported having an eye check in the last 12 mo. Of these, 52 (67.5%) did so in an ophthalmology clinic, 17 (22%) in retinal screening, three (3.9%) in an optician, three (3.9%) went to both ophthalmology and retinal screening, and two (2.6%) attended an ophthalmology and optician.

Diabetic foot screening

Figure 2 shows foot check uptake in the patients surveyed. Seventy (83.3%) patients recalled having a foot check in the previous 12 mo. Of these, 33 (47.1%) were carried out by a practice nurse, 14 (20%) by a diabetes specialist nurse, 11 (15.7%) by the general practitioner (GP), eight (11.4%) by a chiropodist, and four (5.7%) had been a renal nurse, a diabetes consultant, a junior doctor, or unknown person at a foot clinic.

DISCUSSION

Screening programmes have an important role in the prevention and early detection of retinopathy and neuropathy. We are unaware of any previous studies investigating the uptake of screening programmes in haemodialysis patients. In the United Kingdom in 2012-2013, 80.2% of patients offered diabetic eye screening attended. Recent recommendations suggest that is should be possible for a minimum of 85% of those offered digital retinal screening to attend. Screening uptake in 2012-2013 was lower than the results of our study, where we found that 91.7% of patients attended an eye check in the previous last year, suggesting that patients with diabetes on haemodialysis are aware of the need to undertake eye checks on a regular basis.

The United Kingdom National Diabetes Audit 2015-2016, found that 86.7% of patients with diabetes had foot surveillance that year[7], which was slightly

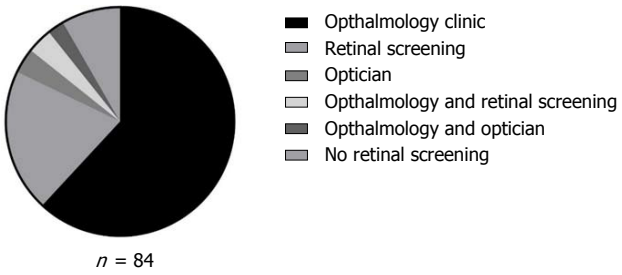

Figure 1 Retinal screening in the cohort.

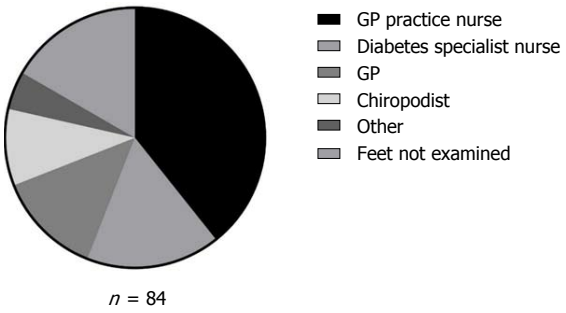

Figure 2 Diabetic foot checks in the cohort. GP: General practitioner.

higher than in our patient survey (83.3%). This is of some concern, particularly as patients with diabetes on haemodialysis are at high risk of foot problems. Recent guidelines recommend that patients have their feet screened every 3 mo with a locally agreed tool, and by staff on the dialysis unit[4].

In the United Kingdom, co-ordination of screening programmes for eyes and feet are led in the community by primary care health professionals. Retinal screening programmes are locally commissioned within Clinical Commissioning Group, and call and recall is organised by review of primary care records. Most retinal screening occurs *via* the retinal screening programme, although patients with established significant retinopathy may attend a medical retinal clinic as well. In the present study, it was found that the ophthalmology clinic was the most common place for eye checks, accounting for 67.5% of all patients. This is unsurprising as many patients on haemodialysis also have other microvascular complications such as retinopathy. A small proportion of patients had eye checks carried out by an optician, which, whilst useful, means that such patients may not be accessing a formal retinopathy screening programme. Interestingly, 7.1% of patients had an eye check carried out more than once in the past year, suggesting some duplication.

Foot checks for people with diabetes are generally performed by trained clinical staff in the primary care centre, which is often the practice nurse. Our study confirmed that nurses in the community were the most common group to carry out diabetic foot checks, with 67.1% of foot checks carried out by the nurses in primary care. Very few patients stated that their feet had ever been examined on the dialysis unit during

dialysis. Patients on haemodialysis have logistical difficulties that make it difficult for them to attend appointments elsewhere. Perhaps this may account for patients missing screening appointments. A lack of co-ordination between the health care professionals caring for the patients may have also resulted in missed screening opportunities, as it is assumed that they have been carried out elsewhere. Patients spend significant amounts of time on dialysis, and this may provide an excellent opportunity for screening of feet and eyes to be undertaken opportunistically, as well as reducing the need for patients to attend hospital in between dialysis sessions. This is specifically mentioned as an important aim in recent United Kingdom guidelines, and clearly needs to be addressed in our haemodialysis unit[4]. These guidelines recommend that annual checks are documented, and made available to all those involved in the care of these patients.

The introduction of a robust system of documentation, would ensure that individuals involved are aware of recent checks and when they last took place, avoiding unnecessary duplication. Furthermore, access to a named link worker on the dialysis unit who would ensure that screening is carried out, which could ensure that patients have received eye and foot screening, and are also educated in looking for early signs of significant foot problems, and highlight these to health professionals at an early stage. Inter-professional learning between diabetes and renal specialists may facilitate improvements in care.

There are some limitations to this study, including a small patient cohort and the fact that it was carried out at a single tertiary centre. Patients with communication difficulties were excluded from the study, and it is possible that this group of patients may have had difficulty accessing healthcare, and may also be more likely to miss screening appointments. The study did not examine the barriers to patients attending screening appointments.

Patients with diabetes on dialysis are at risk of microvascular complications, and due to logistical issues have difficulties attending other appointments. Most patients had an eye check in the last year, with a lower percentage of recalling a foot check in the last year. It is hoped that the introduction of recent guidelines will improve the uptake of screening.

COMMENTS

Background

Patients with diabetes on haemodialysis are at high risk of diabetes complications including foot and eye problems. It is not known whether patients with diabetes on haemodialysis attend regular screening appointments for foot and eye checks. This survey aimed to determine this information.

Research frontiers

It is increasingly recognised that prevention of diabetic complications in patients on haemodialysis is important. At the moment, it is unknown whether improving glucose control or other risk factors will reduce morbidity and mortality in such patients.

Innovations and breakthroughs

Recent United Kingdom guidelines suggest a more proactive approach to managing patients with diabetes on haemodialysis. It is hoped that with more structured care, better outcomes will be seen.

Applications

The authors show that most patients with diabetes on haemodialysis attend for eye checks, but that foot checks may be neglected. The authors propose that foot checks on dialysis would be an effective way to ensure proactive management of foot problems in patients on dialysis.

Peer-review

Mothojakan *et al* report the findings of a retrospective study of whether foot and eye screening is being done on diabetic patients undergoing hemodialysis. The paper has been revised in light of a previous review and is well written, easy to follow and without any obvious errors or unfounded claims.

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