Prevalence of anaemia and its association with renal function in diabetic patients from south of Libya

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Abstract: Anaemia is a common complication of diabetes mellitus (DM), particularly in those with renal impairment. Despite this fact, most of diabetic patients in our community are rarely tested for anaemia. Thus, we aimed to examine the prevalence of anaemia and its relation to renal function among diabetic patients from south of Libya. Two hundred diabetic patients attended the medical outpatient clinic of Murzuk general hospital and Brack general hospital were included in this study. The control group consisted of 75 healthy volunteers. fasting blood sugar (FBS), glycatedhaemoglobin(HbA_{1C}), haemoglobin (Hb), creatinine and estimated glomerular filtration rate (eGFR) were assessed for all participants. Data showed that HbA_{1C} (%) were greater ($p < 0.001$) in Type1 DM (8.11 ± 2.2) and Type2 DM (9.3 ± 2.8) than the control group (6.1 ± 0.9). Hb (g/dl) levels of Type1 and Type2 patients (12.6 ± 1.9 and 12.8 ± 1.7) were significantly lower ($p < 0.05$) than the control group (13.4 ± 1.4). The eGFR values were categorized as ≥ 90, 60 - 98 and < 60 ml/min/1.73 m^2. According to these categories, patients with type 1 and type 2 at the 3 levels of descending eGFR were 45%, 23% and 32%; 46%, 23% and 31% respectively, compared to 70.7%, 13.3% and 16% of the control group. Similarly, the prevalence of anaemia among type1 and type 2 patients at the 3 levels of descending eGFR were 28.9%, 34.8% and 31.3%; 30.4%, 39.1% and 41.9% respectively, compared to 16.9%, 10.0% and 25% for the control group. In all groups, Hb levels correlated significantly ($p < 0.05$) with eGFR ($r = + 0.43$). Anaemia is highly prevalent in diabetic patients and significantly associated with renal function. Therefore, anaemia should be assessed and continuously monitored even to those without overt renal dysfunction.

Keywords: anaemia, diabetes, eGFR, renal function, Libya.

Introduction

Diabetes mellitus (DM) is increasingly becoming a major chronic disease burden all over the world. In 2014, 9% of adults 18 years old and older have diabetes (1). In 2012, an estimated 1.5 million deaths were directly caused by diabetes; more than 80% of diabetes deaths occur in low and middle-income countries (2). Diabetes mellitus is the most common risk factor for chronic kidney disease (CKD), and is the leading cause of end-stage renal disease (ESRD) (3); consequently, it is the most common cause of renal anaemia (4, 5). Although it is known that aneamia is common in patients with CKD, the impact of diabetes on the degree of anaemia and severity of kidney dysfunction in diabetic patients has not been well understood. A number of studies have reported the prevalence of anaemia in diabetic people and suggested that up to 25% of those have previously unrecognized anemia (4, 6). In

diabetic patients with CKD, anaemia occurs at early stages and is more severe compared to non-diabetics CKD (7). Patients with diabetic nephropathy commonly have a greater degree of anaemia in relation to their degree of renal impairment than from those causes of renal failure (4, 6). Moreover, anaemia is strongly associated with more rapid progression of renal disease in diabetic patients (8). Some studies have demonstrated an association between Haemoglobin (Hb) concentration and kidney function in diabetic patients; A lower Hb is significantly associated with a more rapid decline in the glomerular filtration rate (GFR)(4, 9, 10). It has been reported that a GFR of < 60ml/min is strongly associated to a higher prevalence of anaemia in diabetic patients with CKD (4). On the other hand, anaemia also occurs in diabetic patients even with a GFR of > 60 ml/min (5).

Diabetes and its related complication form a major component of non-communicable disease in Libya. The prevalence of diabetes was estimated to be 16% among adults aged 18 years and older; and this figure may increase up to 23.7% if we consider the undiagnosed cases among the adult population (11). Libya had also a relatively high prevalence (624 pmp) and incidence (282 pmp) rates of dialysis-treated end stage renal diseases (ESRD), where diabetes mellitus was the most common cause (26.5%) among previously and newly diagnosed patients (12, 13). Most importantly, the observed incidence rate was substantially higher in the south compared to other geographical regions of Libya (12). While anaemia is one of the most common chronic complications of diabetes, it has been commonly overlooked and at times ignored in the management of diabetes; furthermore, most of the diabetic patients in the south of Libya are rarely tested for anaemia and are unaware of the link between anaemia and kidney disease. Thus, the aim of this study was to investigate the prevalence of anaemia and its relation to renal function in diabetic patients from the South of Libya.

Materials and Methods

Study design: Two hundred diabetic patients (71 males and 129 females) attending the medical out-patient clinic of Murzuk General Hospital and Brack General Hospital for a routine check-up were used as samples in this study. In each health care facility, Fifty patients with type 1 diabetes mellitus and fifty (50) with type 2 were utilized. The age ranges from 19 to 80 years old. For the purpose of comparison, a control group consisted of 75 healthy volunteers (33 males and 42 females) aged between 20 to 64 years old were also employed. Patients who received treatment for anaemia in the last three months were excluded from the study.

Samples and analysis: Venous blood samples were withdrawn from all samples after an overnight fasting (12 hours) and were processed for the determination of fasting blood sugar (FBS), glycatedhaemoglobin (HbA_{1C}), haemoglobin (Hb), and creatinine. FBS was measured by commercial Kit (Biocon) based on glucose oxidase method using glucose analyzer (BECKMAN, USA); glycatedhaemoglobin (HbA_{1C}) percentage was determined according to a boronate affinity chromatography method using NYCO Card reader II; haemoglobin level was measured using Sysmex KX21N hematology analyzer, Japan; creatinine was measured by commercial kit (Biocon) based on Jaff method, using creatinine analyzer (BECKMAN, USA). Urinary albumin excreation was also measured (Medi-test combi 11, Germany).

Body weight (to ± 100 g) was measured using electronic calibrated scale. Estimated glomerular filtration Rate (eGFR) was calculated using the Cockeroft-Gault equation [(140-age)× weight(kg)]/ [serum creatinine(mg/dl) × 72] × 0.85 if female (14). Patients with Hb level of < 13g/dl (males) and < 12 g/dl (females) were classified as anaemic as per WHO criteria (15).

Statistical analysis: Data were expressed as mean (± standard deviation), and analyzed by student *t*-test and ANOVA as appropriate. The SPSS statistical software was used for analysis. Correlation was tested using Pearson's correlation. For all analysis, P value < 0.05 was considered statistically significant.

Results

This study consisted of 275 samples, of whom 200 had DM, and 75 were healthy volunteers. Of the diabetic patients 35.5% were males and 64.5% were females, aged between 19 to 80 years old (49 ± 13.2). Both type 1 and type 2 DM had an equal distribution of 50% each. The duration of diabetes varied from 1.5 to 31 years. Forty-four percent of the healthy volunteers (control group) were males and 56% were females; aged from 20 to 64 years old (33.6 ± 10.8).

Glycemic status: The mean concentration of FBS in Type1 DM, type2 and control subjects were 154.5 ± 78.3, 186.9 ± 66.5 and 91.01 ± 12.8 mg/dl, respectively (table1). The mean values of glycated heamoglobin (HbA_{1C}) in the blood of type 1 DM, type 2 and the control group were 8.11 ± 2.2, 9.26 ± 2.8 and 6.05 ± 0.9 % respectively (table 1). The mean values of FBS and HbA_{1C} in both of the diabetic groups were significantly higher than the control group ($p < 0.001$); however, the mean values of both variables were significantly lower in patients with type 1 DM compared to those with type 2 ($p < 0.01$). In addition, results showed that 77% of patients with type 1 DM and 84% with type 2, had a HbA_{1C} levels of more than 7% (the recommended value by ADA), which reflects a poor blood glucose control in these patients.

Table 1: Mean values of FBS, HbA_{1C} , eGFR, creatinine and presence of albuminuria in diabetic and control groups. Date are expressed as mean±SD.

Variables	Type 1 DM (n=100)	Type 2 DM (n=100)	Contro l(n=75)
FBS (mg/dl)	154.5 ± 78.3	186.9 ± 66.5	91.01 ± 12.8
HbA_{1C} (%)	8.11 ± 2.2	9.29 ± 2.8	6.05 ± 0.9
eGFR (ml/min/1.73m^2)	84.03 ± 37.1	86.7 ± 36.4	105.9 ± 31.4
Creatinine (mg/dl)	0.94 ± 0.4	0.98 ± 0.5	0.76 ± 0.3
Albuminuria [n(%)]	44(44%)	45(45%)	Nil (0%)

Renal function: the mean serum creatinine concentration in patients with type 1 DM and type 2 (0.94 ± 0.4 and 0.98 ± 0.5 mg/dl, respectively) were significantly higher ($p < 0.01$) than that of the control group (0.76 ± 0.3 mg/dl) (table 1). Interestingly, 38%, 33% and 14% of patients with type 1 DM, type 2 and control group, respectively, had a serum creatinine concentration above the normal values (> 1.2 mg/dl for males and > 1.0 mg/dl for females).

Estimated glomerular filtration rate was assessed using the Cockcroft-Gault formula and expressed per 1.73 m^2 of body surface area. The overall mean values of

eGFR in type 1 DM, type 2 and control subjects were 84.03 ± 37.1, 86.7 ± 36.4 and 105.9 ± 31.4 ml/min/1.73 m^2 respectively (table 1). Significant differences existed between both of the diabetic groups and the control group ($p < 0.001$). Based on the ranges of kidney disease outcomes quality initiative (K/DOQI) guidelines, renal function was stratified according to eGFR values (ml/min/1.73 m^2) using the following cut-points: ≥ 90 (stage I: normal renal function), 60-89 (stage II: mildly impaired renal function) ; 30 - 59 (stage III: moderately decreased renal function); 15 - 29 (stage IV: severely impaired renal function); < 15 (stage V: kidney failure) (16). We grouped those with eGFR < 30 ml/min with those having moderately impaired renal function (stage III), because of the small number of such individuals (n = 5). Subsequently, eGFR values were classified into 3 main categories as the following: ≥ 90 (stage I: normal renal function), 60-89 (stage II: mildly impaired renal function); < 60 (stage III: moderately impaired renal function). According to these categories the distribution of patients with type 1 and type 2 DM at the 3 levels of descending eGFR were 45%, 23% and 32%; 46%, 23% and 31%, respectively, compared to 70%, 13.3% and 16% of the control group (table 2). Our results showed that nearly 31.5% of the diabetic patients have moderate renal impairment (eGFR < 60 ml/min/1.73 m^2), while 23% were found to have mild renal impairment (eGFR 60-89 ml/min/1.73 m^2); However, a higher percentage of 45.5% had normal renal function (eGFR ≥ 90 ml/min/1.73 m^2). The mean eGFR values for Type 1 DM, Type 2 and the control group at the 3 stages of descending eGFR were the following: Stage I (120.6 ± 14.2, 121.5 ± 15.1 and 124.4 ± 13.2); stage II (72.2 ± 9.1, 74.8 ± 9.9 and 68.9 ± 9.2); stage III (40.9 ± 9.3, 43.8 ± 9.2 and 54.9 ± 5.8 ml/min/1.73 m^2) respectively (table 2). There were no significant differences ($p > 0.05$) between the different groups at the individual GFR stages, except at stage III (moderate renal impairment) where there were a significant difference ($p < 0.001$) between each of the diabetic groups and the control group.

Table 2: Prevalence of anaemia and albuminuria in various stages of renal function based on eGFR (by K/DOQI). Data are expressed as mean ± SD.

Variable (Mean ± SD)	eGFR (ml/min/1.73 m^2)	Albuminuria (%)	% of anaemia
Stage I (normal)			
Type 1 DM (45%)	120.6 ± 14.2	38.6%	28.9%
Type 2 DM (46%)	121.5 ± 15.1	44.5%	30.4%
Control (70%)	124.4 ± 13.2	Nil (0%)	16.9%
Stage II(mild)			
Type 1 DM (23%)	72.2 ± 9.1	25 %	34.8%
Type 2 DM (23%)	74.8 ± 9.9	22.2%	39.1%
Control (13.3%)	68.9 ± 9.2	Nil (0%)	10%
Stage III (moderate)			
Type 1 DM (32%)	40.9 ± 9.3	36.4 %	31.3 %
Type 2 DM (31%)	43.8 ± 9.2	33.3%	41.9%
Control (16.7%)	54.9 ± 5.8	Nil (0%)	25%

The prevalence of albuminuria in both types of diabetic patients showed similar pattern. Overall, 44% with type 1 DM and 45% with type 2 had an elevated albuminuria, of whom 38.6%, 25% and 36.4% with type 1 DM; 44.5%, 22.2% and 33.3% with

type 2 had normal renal function, mild renal impairment and moderate renal impairment respectively. By comparison, none of the control subjects showed presence of albuminuria (table 1).

Haemoglobin level and prevalence of anaemia: the mean haemoglobin levels were 12.6 ± 1.9 g/dl (14.4 ± 1.5 for males and 11.9 ± 1.5 for females) in type1 DM and 12.8 ± 1.7 g/dl (13.7 ± 2.0 for males and 12.2 ± 1.3 for females) in type 2 patients, compared to 13.4 ± 1.4 g/dl (14.5 ± 1.1 for males and 12.6 ± 1.1 for females) for the control group (table 3). Overall, the mean haemoglobin levels in type 1 DM and type 2 patients were significantly lower than the control group ($p < 0.05$). The haemoglobin values in diabetic patients and the control group gradually decreased along with decreasing GFR. The difference was statistically significant ($p < 0.05$) between stage 1 and stage 3 of both of the diabetic types, however there was no significant difference between the control group at the individual GFR stages. On the other hand, the mean Hb values in type 1 and type 2 DM patients were significantly lower ($p < 0.05$) than that of the control group at the moderate renal impairment stage, but did not significantly differ in the other GFR stages. In this study, samples were categorized as anaemic as per the WHO criteria of Hb < 13 g/dl if male and < 12 g/dl if female. Using this criterion, 31%, 36% and 17.3% of type 1 DM, type 2 and the control group respectively were categorized as anaemic (Table 3). Our results indicated that the prevalence of anaemia in diabetic patients was approximately double that in non-diabetic.

Table 3: Mean heamoglobin (Hb) values in diabetic and control groups.
Data are expressed as mean ± SD.

Variables	Type 1 DM	Type 2 DM	Control
Hb (g/dl) in all samples	(n = 100)	(n = 100)	(n = 75)
All	12.6 ± 1.9	12.8 ± 1.7	13.4 ± 1.4
Male	14.4 ± 1.5	13.7 ± 2.0	14.5 ± 1.1
Female	11.9 ± 1.5	12.2 ± 1.3	12.6 ± 1.1
Hb (g/dl) in anaemic subjects	(n = 31)	(n = 36)	(n = 13)
All	10.6 ± 1.3	11.3 ±1.4	11.8 ± 0.7
Male	12.2 ± 1.1	11.8 ± 2.1	12.6 ± 0.4
Female	10.1 ± 1.01	11.1 ± 0.7	11.3 ± 0.4

Anaemic type 1 DM samples had a mean Hb levels of 10.6 ± 1.3 g/dl (12.2 ± 1.1 for males and 10.1 ± 1.01 for females) and 11.3 ± 1.4 g/dl (11.8 ± 2.1 for males and 11.1 ± 0.7 for females) in type 2, compared to a mean value of 11.8 ± 0.7 g/dl (12.6 ± 0.4 for males and 11.3 ± 0.4 for females) for the control group (table 3). The mean Hb levels of the anaemic individuals were significantly lower ($p < 0.05$) than the non-anaemic samples, moreover the mean Hb values of the anaemic patients with type 1 DM were significantly lower ($p < 0.05$) compared to the anaemic samples found in the control group, but those with type 2 did not differ significantly as compared to the anaemic subjects in the control group ($p = 0.16$). The prevalence of anaemia by K/DOQI category of renal function was examined for diabetic samples and the control group. Anaemia prevalence was significantly higher in type 1 DM and type 2 patients compared to the control samples at the normal renal function stage (28.9% and 30.4% vs. 16.9%, respectively, $p < 0.001$); mildly impaired renal function stage (34.8% and 39.1% vs. 10%, respectively, $p < 0.001$) and moderately impaired renal function stage (31.3% and 41.9% vs. 25%, respectively, $p < 0.001$) (table 2). In samples with anemia, 67.7% of the type 1 DM and 63.9% of type 2, had a normal or mildly impaired renal function (eGFR ≥ 60 ml/min), whereas 32.3% and 36.1%, respectively had moderately impaired renal function (eGFR < 60 ml/min). Similarly 38.7% and 30.6% of anaemic patients with type 1 DM and type 2 respectively had elevated albuminuria. Moreover, 25.8% of the type 1 DM and 33.3% of type 2 anaemic patients had abnormally high serum creatinine concentration.

In the whole diabetic groups, there was a statistically significant correlation of Hb levels with renal function as measured by eGFR ($r = +0.43$, $p < 0.05$) and glycemic state as measured by HbA_{1C} ($r = +0.14$, $p < 0.05$); but not correlated with serum creatinine ($r = - 0.07$, $p = 0.61$) or type of DM ($r = 0.053$, $p = 0.45$). Moreover, eGFR was not correlated with HbA_{1C} except at stage III of renal function (eGFR < 60 ml/min)($r = -0.36$, $p < 0.05$).

Discussion

In this study, the prevalence of anaemia and its association with renal function was evaluated among diabetic patients attending the medical out-patients clinics of two general hospitals located in the South of Libya. Data presented in this study showed that 31% and 36% of patients with type 1 DM and type 2 DM, respectively, were anaemic. These findings indicated that the prevalence of anaemia among DM patients is relatively higher than those reported in other countries such as Ethiopia (19%) (4), Ireland (13%) (8), USA (12%) (17), UK (23%) (18) and Australia (20%) (19). However, it is considerably lower than that reported by another study conducted in UK (41%) (7). The prevalence of anaemia varies depending on both the population studied and the definition used. One of the latest studies that is most comparable to our study is the one conducted in Ethiopia, which defined anaemia according to the WHO criteria as (< 13 g/dl for men and < 12 g/dl for women), and found that the prevalence of anaemia was 19% (4). The relatively high prevalence of anaemia observed in this study could be attributed to the poor metabolic control seen in these patients as indicated by the high HbA1c levels; since hyperglycemia is significantly related to chronic diabetes complications (20). Our results showed that

more than 75% of diabetic patients had HbA1c levels above 7% and that is suggested to be due to non-compliance with diet, drugs and lack of knowledge on diabetes and its complications. Lack of diagnostic facilities as well as insulin and other hypoglycemic therapy in the south of Libya especially during the last 3 years may also contribute to this high prevalence rate. The renal function tests showed that 35.5 % of the diabetic samples had abnormally high serum creatinine, 31.5% with moderately decreased eGFR and 44.5% with elevated albuminuria. This finding is in agreement with some previous studies done in other countries (4, 19). Some other studies have demonstrated an association between the prevalence of anaemia and kidney function in diabetic patients (4, 7, 8). The results of this study showed that while about 33.5% of the diabetic patients were anaemic, approximately 34.2% and 34.7% of those anaemic patients had moderately decreased eGFR and /or elevated albuminuria. In addition, significant correlation also existed between Hb levels and renal function. This finding is in agreement with similar works conducted in Australia and UK where 33% to 36% of anaemic patients had evidence of moderately impaired renal function(eGFR < 60 ml/min/1.73 m^2) (19, 21) and the prevalence of elevated albuminuria varied between 27% and 43% (19). By contrast, studies done in UK (7) and Ethiopia (4) reported that 15.6% and 13.8% of anaemic patients with DM had eGFR below 60 ml/min/1.73 m^2. It is clear that anaemia is associated with albumin-uria, an early marker of microvascular inflammation and damage (18); however, it has also been shown that even in the absence of albuminuria, anaemia in diabetic patients is almost due to impaired renal function (9). This strong relationship between renal function and anaemia in diabetic patients indicates the unique vulnerability of renal microcirculation to damage in DM (18). The degree of anaemia in diabetic patients has been associated with a number of factors including GFR, albuminuria and HbA_{1C} (4, 8). The current study is in agreement with these findings as eGFR and HbA_{1C} were correlated with Hb levels, however, serum creatinine level and the Type of DM were not correlated with Hb levels. This study also showed that renal function (eGFR) was well correlated with HbA_{1C} at the moderately impaired renal function stage.

Furthermore, the prevalence of anaemia was found to be significantly higher and the mean Hb values were significantly lower in diabetic patients than in non-diabetic individuals. As assessed according to the different stages of renal function, the prevalence of anaemia was significantly higher among diabetic patients than in non-diabetics in all stages of renal function. Similar observation was also reported by Al-Khoury et al. (7). Moreover, Hb level was significantly lower in diabetic patients than the non-diabetics only at the moderate renal impairment stage (eGFR < 60 ml/min/1.73 m^2). Similar observations was made by El-Achkar et al. (17). In contrast, Al-Khoury et al. (7), observed that Hb values were significantly different between subjects with and without diabetes mellitus at all stages of renal function. Low levels of erythropoietin in patients with either type1 or type 2 DM and anaemia had been reported (6, 22). It has shown that about 50% of patients with type 1 DM, nephropathy and serum creatinine < 2 mg/dl had unexplained anaemia with relatively low erythropoietin levels, compared to 0% in non-diabetic patients even with glomerulonephritis (6). There is evidence that failure to increase

circulating erythropoietin levels in response to falling haemoglobin concentration is the dominant factor in the genesis of anaemia associated with diabetic nephropathy (22). Erythropoietin depletion and anaemia do not normally occur in non-diabetic renal disease until glomerular filtration rate is decreased below 20-40 ml/min (23). This study is in congruence with some other studies, that found a high prevalence of anaemia in diabetic patients with normal or mildly impaired renal function (eGFR > 60 ml/min) (5, 8, 21). In addition, this study and previous studies demonstrated a strong correlation between Hb and eGFR even at normal or mildly impaired renal function(7, 8, 17). It has been suggested that erythropoietin deficiency occurs earlier in diabetic nephropathy compared to other causes of nephropathy, and this may be caused by a relative resistance or absolute deficiency of erythropoietin production by the kidney (23). Regardless of the cause, our findings and others showed that anaemia also occurred in diabetic patients with apparently normal renal function; thus screening for anaemia should be carried out for DM patients regardless of their current state of renal function.

In conclusion, this study is one of the few studies that were performed about DM and its complications since the beginning of conflict in Libya. The high prevalence rate of anaemia observed in this study supports the notion that DM and its complications constitute a major health care challenge in Libya. This requires urgent action by the local healthcare authorities so as to promote prevention, early detection and referral of DM patients with anaemia to specialized medical centers. Public awareness through health education must be initiated to promote health and prevent the debilitating effects of this disease. These observations in the South of Libya require further investigation and have important implications for future health-care provision.

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