The relationship of depression and anxiety among diabetic patients with changes in the components of lipid profile

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Diabetes, depression, anxiety, Saudi Arabia, lipid profile
Abstract
Introduction our study aimed to investigate the presence of depression and anxiety symptoms in diabetic patients and their association with various components of lipid profile.

Methods 428 patients with diabetes mellitus joined our study. Their demographic and lipid profile measurements were collected. The screening questionnaire HADS was used to evaluate level of depression and anxiety. An age matched control group consisting of 50 individuals were taken and their lipid profiles and depression and anxiety levels were determined.

Results it was found that 22.4% of the sample showed marked depressive symptoms and 28.5% showed marked anxiety symptoms. We found that: depression was associated strongly but not significantly (P=0.057) with lower high density lipoproteins, and associated significantly (P=0.036) with lower total cholesterol level. In addition, anxiety was associated significantly (0.000) with lower high density lipoproteins and was associated significantly (P=0.004) with higher triglycerides level. There was insignificant association between all components of lipid profile and either depression or anxiety levels in the control group.

Conclusion Depressive and anxiety symptoms were common among diabetic patients. Depression was related to lower high density lipoproteins, and to lower total cholesterol level. Anxiety was strongly related to lower high density lipoproteins and to higher triglycerides level. This relationship was specific to patients with diabetes mellitus in our study.

Background
Psychiatric disorders including mood and anxiety disorders and their relation to cardio-vascular disease were an interesting area of research but this relation is not clear [1]. Many studies found a relation between low cholesterol level and major depression [2,3,4] and in a study, lipid profile was related negatively to suicidal attempts [5].

Another study including 300 females showed that depressive symptoms were two fold with total cholesterol less than 180mg/dl but other studies didn’t find this relation [6,7,8]. Regarding the anxiety disorders, it was found that panic disorder patients had significantly higher cholesterol values compared with the patients with major depressive disorder and healthy controls [9]. Also, increased
total cholesterol, triglycerides, LDL- cholesterol and decreased HDL- cholesterol were discovered in Vietnam veterans with post traumatic stress disorder [10]. Furthermore, in the Netherland study of depression and anxiety (NESDA), lower high density lipoproteins and higher triglycerides levels were found in patients with major depression compared to controls and subjects in remission from depression [11].

Many studies found that depression and accordingly psychiatric disorders were associated with disturbed glycemic control [12,13] and increased complications including cardio-vascular complications and also increased mortality [14,15,16,17]. Psychological distress is common among diabetic patients; and about 30% of patients with type 2 diabetes mellitus have depressive symptoms [18,13] and 40% have increased anxiety symptoms [19]. In this population, there may be a double effect on lipid profile caused by diabetes mellitus and either depression or anxiety. In the present study, we aimed to study the relationship of depression and anxiety that are associated with diabetes mellitus and the various components of lipid profile and to explore if there is a difference in lipid profile in diabetic patients with and without associated depression or anxiety.

Methods
Setting
This study is a cross-sectional study that was ethically approved by the Ethical Committees at the College of Medicine, Aljouf University, and Ministry of Health, in Al-Jouf, Saudi Arabia. Data were collected during the months from February to May, 2016 at the diabetic centers of king Abdulaziz specialist hospital, Domat Al-Jandal and Prince Muteb General Hospitals in the north of Al-Jouf region in Saudi Arabia.

Participants:
Before obtaining the data, individuals were informed about the aim of the study and the how to complete the questionnaires. They were assured that all the information will be anonymous and absolutely confidential. Also, it was explained that the results would be used to enhance science evolution. The sample was obtained randomly. Patients with a history of neurological disorders, such as, stroke and with a history of psychiatric disorders were excluded from the study. Also, Patients with
infectious conditions that cause disruption in their diabetes and women with gestational diabetes were also excluded. Furthermore, patients who take statins that lower serum lipid profile was excluded from our study as statin treatments may affect depression or anxiety levels [20,21]. A total number of 428 patients were included with either type I or type II diabetes. An age matched control group was taken that included 50 individuals.

Intervention:
The demographic data and clinical measures of the included Saudi patients with diabetes mellitus were taken from the data form that was handed to patients to be filled by the patient and by the attending physician. This form consisted of items such as: job status, age of the patient, physical activity, smoking habits, duration of diabetes, type of treatment taken, educational status and marital status. The research was approved by the ethical committee in the college of medicine, Jouf University.

The blood samples were taken after a 12-hour fasting to estimate lipid profile. Serum total cholesterol and triglycerides were evaluated by spectrophotometry in auto analyzer. HDL-C was measured by Dextran sulfate Mg2+ precipitation procedure [22] (Pacific Biomarkers company, 645 Elliott Ave W, Suite 300 Seattle, WA 98119, USA). LDL-C was measured using the Friedwald equation [23]. Serum lipid profile was estimated for both the diabetic and control groups.

Depression and anxiety were evaluated using the hospital anxiety and depression scale questionnaire (HADS) [24]. The questionnaire was given to the patient in the local simple Arabic language and this questionnaire was validated [25,26]. HADS questionnaire comprised 14 items, each item has four levels. It consists of 7 questions evaluating anxiety and 7 evaluating depression. The maximum sum of answer results was 21 for each scale. HADS determines the score of symptoms within the last 10 days. The questionnaire was made to exclude false positive results in patients with physical disorders [27,28]. Scores of 11 or more on either subscale are a consideration of “caseness” of psychiatric illness and a score of 8-10 was considered as borderline, while a score of 7 or less is normal [29,30]. Of the 450 questionnaires given to the patients, 428 were valid for the study. Depression and anxiety levels were calculated for both the diabetic and control groups.
Statistical analysis

Data was written manually into a database and managed before analyses. The Statistical Package for the Social Science (SPSS) version 20 software was used for analysis. Items that were not answered by respondents were excluded from the database. Mean values, standard deviations, frequencies and proportion percentages were calculated for continuous and categorical variables. One way ANOVA test was performed to compare means and standard deviations between different groups. The significance was determined as $p < 0.05$.

Results

428 diabetic patients were studied from which 57% were men and 43% were women. 76.4% of the sample were married and 23.6% unmarried. Regarding the educational level, 43.7% were educated to preparatory school level or lower, 25.5% to secondary school level and 30.8% had university education. The mean age of participants was 52 (51.6 ± 14.2). Furthermore, the mean scores were 8 (7.9 ± 3.79) for depression and 8 (7.99 ± 4.27) for anxiety. About 22.4% of the sample had significant depressive symptoms (caseness, score ≥11) and 28.5% had significant anxiety symptoms (score ≥11). 117 (27.3%) were taking antidiabetic medications only and 311 (72.7%) were taking antidiabetic medications in addition to any other form of pharmacotherapy (including antihypertive drugs, antiplatelets, aspirin, etc.) (Table 1)

- insert table 1 here -

It was found that low density lipoproteins (LDL) mean and St. deviation was (109.2±35.9) and that high density lipoproteins mean and St. deviation was (37.2±15.5). Also, we found that triglycerides mean and St. deviation was (156.7±81.3) and total cholesterol mean and St. deviation was (180±46.6) (Table 1).

The effect of taking any pharmacotherapy in addition to antidiabetic treatment on anxiety severity was insignificant ($P = 0.160$) (table 2) and also was insignificant ($P = 0.087$) regarding depression severity (table 3).

- insert table 2 here-

- insert table 3 here-
Differences between various groups of depression severity (normal, borderline, caseness) regarding LDL were non significant (P = 0.599), whereas depression was strongly (but not significantly) associated with lower HDL (P = 0.057). Also, difference regarding TG was non significant (P = 0.88) between groups. However, depression was significantly associated with lower level of total cholesterol (P = 0.036) (Table 4).

- insert table 4 here -

Anxiety was significantly associated with lower HDL levels (P = 0.000) and with significantly higher TG levels (P = 0.004). Neither LDL (P = 0.076) or total cholesterol (P = 0.70) were associated with anxiety (Table 4).

The anxiety scores on HADS was significantly negatively correlated with HDL levels (P = 0.00) and was significantly positively correlated (P = 0.004) with triglycerides levels. On the other hand, depression scores showed insignificant negative correlation with cholesterol levels (P = 0.66) and also insignificant correlations with all other components of lipid profile.

Regarding the age matched control group, there was insignificant association between depressive severity groups and all components of lipid profile (table 5). Similarly, there was insignificant association between anxiety severity groups and all components of lipid profile (table 6).

- insert table 5 here-
- insert table 6 here-

**Discussion**

Most of the patients were taking pharmacotherapeutic treatments in addition to antidiabetic treatments and it was found that the effect of this additional medications was insignificant on either depression severity (P = 0.087) or anxiety severity (P = 0.16).

We found that depression was strongly associated with lower HDL (P = 0.057). Netherland study of depression and anxiety found that lower HDL and higher TG levels were detected in patients with major depression compared to controls and in patients in remission from depression [11]. Furthermore, one population based case control study found that long term depression is associated with low HDL, high TG and a high LDL/HDL ratio [30].
We also found that depression was significantly associated with lower cholesterol (P = 0.036). Many studies reported an association between low cholesterol level and major depression (2,3,4) and in a study lipid profile correlated negatively with suicidal attempts [5]. Another study including 300 females found that depressive symptoms were twice with total cholesterol lower than 180mg/dl but other studies didn’t find this relation [6,7,8]. However, one population based study found that increased depressive symptoms was associated with high total cholesterol [31]. This may point to the complex relationship between cholesterol and depression although differences in methodology and characteristics of the sample may to some extent explain this complex relation. Depression usually affects health behaviors causing decrease in appetite and in physical activity and so may affect the association between components of serum cholesterol and depressive symptoms [32,33] and as an example the association between low HDL and depression may be due to decreased intake of long chain polyunsaturated fatty acids associated with depression [32]. Also, psychological distress and depression causes dysregulation of hypothalamo-pituitary-adrenal axis that may lead to disturbances in lipid profile.

In addition, we found that anxiety was associated with significantly lower HDL (P = 0.000) and significantly higher TG (P = 0.004). It was found that increased TG, LDL and decreased HDL affected Vietnam veterans with chronic post traumatic stress disorder [10] Comorbid anxiety may increase the levels of circulating adrenaline and noradrenaline and cause increase in lipoprotein lipase activity, thus increasing the serum cholesterol and triglyceride concentrations [34,35]. Another study exploring the effect of treating comorbid anxiety in diabetic patients on lipid profile found that the high-density lipoprotein cholesterol level increased significantly after the administration of antianxiety drug, but other components of the lipid profile were the same. The results indicate that the decrease of stress in diabetic patients was associated with increase in high-density lipoprotein levels [36]. Similarly, doing Pearson correlation between depression scores or anxiety scores on HADS and various components of lipid profile, we found that anxiety scores were significantly negatively correlated with HDL levels (P = 0.00) and significantly positively correlated with triglycerides levels (P = 0.004) while depression scores correlated negatively but insignificantly (P = 0.66) with cholesterol.
Regarding the age matched control group, there was insignificant associations between depression and anxiety severity groups and all components of lipid profile which might mean that the relation between serum lipid profile and anxiety or depression was specific to diabetic patients in our study (Table 5 and 6).

The limitations of our study are: Firstly, HADS questionnaire is a screening tool and is not made to diagnose specific psychiatric disorders. Also, there might have been a recall bias by the patients and we tried to decrease this factor by limiting the recall period to 7 days before the filling of the questionnaire. The information regarding age, type of treatment, and duration of diabetes was compared with the data in the medical records.

We advise that Patients with diabetes mellitus with comorbid anxiety or depression will have special attention regarding the assessment and follow up of their cardio-vascular condition. Lipid profile should be performed regularly to these patients to guard against possible high risk of cardio-vascular complications and providing appropriate care and treatment in the presence of disturbances in the lipid profile.

Conclusion
Depressive and anxiety symptoms were common among diabetic patients. Depression was related to lower high density lipoproteins, and to lower total cholesterol level. Anxiety was strongly related to lower high density lipoproteins and to higher triglycerides level. This relationship was specific to patients with diabetes mellitus in our study.

We advise that Patients with diabetes mellitus with comorbid anxiety or depression will have special attention regarding the assessment and follow up of their cardio-vascular condition. Lipid profile should be performed regularly to these patients to guard against possible high risk of cardio-vascular complications and providing appropriate care and treatment in the presence of disturbances in the lipid profile.

Abbreviations
- LDL: low density lipoproteins
- HDL: high density lipoproteins

Declarations

Ethics approval and consent to participate: This study is a cross-sectional study that was ethically approved by the Ethical Committees at the College of Medicine, Aljouf University, and Ministry of Health, in Al-Jouf, Saudi Arabia. Before obtaining the data, individuals were informed about the aim of the study and the how to complete the questionnaires. They were assured that all the information will be anonymous and absolutely confidential. Also, it was explained that the results would be used to enhance science evolution. The informed consent was verbal because some of the participants were illiterate and cannot read or write and the verbal consent was obtained from all participants and was approved by the ethics committee in the college of medicine.

Consent for publication: all authors agreed for publication in BMC psychiatry journal.

Availability of data and material: Data were collected during the months from February to May, 2016 at the diabetic centers of king Abdulaziz specialist hospital, Domat Al-Jandal and Prince Muteb General Hospitals in the north of Al-Jouf region in Saudi Arabia.

Competing interests: The authors declare that there is no conflict of interests.

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Authors contributions: Dr AD collected the data and wrote the article while Dr AA did the statistical analysis of the data. All authors have read and approved the manuscript.

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Tables
Table 1: Socio-demographic and laboratory characteristics of the participating diabetic patients (n = 428). Data shown are mean ± SD and frequencies (n and %).

| Demographic characteristics | Mean ± SD | n (%) |
|-----------------------------|-----------|-------|
| Age: Years                  | 51.6 ± 14.2 |       |
| Gender: Male/female         |           | 244/184 (57/43) |
| Marital status: Single/Married |       | 101/327 (23.6/76.4) |
| Education level:            |           |       |
| Preparatory or less         |           | 187 (43.7) |
| Secondary school            |           | 109 (25.5) |
| University                  |           | 132 (30.8) |
| Depression Score (HADS)     | 7.93 ± 3.79 |       |
| Anxiety Score (HADS)        | 7.99 ± 4.27 |       |
| Depression Severity:        |           |       |
| Normal (≤7)                 |           | 204 (47.7) |
| Borderline (8 - 10)         |           | 128 (29.9) |
| Caseness (≥11)              |           | 96 (22.4) |
| Anxiety Severity:           |           |       |
| Normal (≥7)                 |           | 213 (49.8) |
| Borderline (8 - 10)         |           | 93 (21.7) |
| Caseness (≥11)              |           | 122 (28.5) |
| Anti diabetics medications only |       | 117 (27.3) |
| Antidiabetic medications+ additional medications | 311 (72.7) | |
| LDL                         | 109±35.9 |       |
| HDL                         | 37.2±15.5 |       |
| Triglycerides               | 156.7±81.3 |       |
| Cholesterol                 | 180±46.6 |       |

(Table 2): chi-square calculation between medications and anxiety severity:

| Variable                        | anxiety severity | Total |
|---------------------------------|------------------|-------|
|                                 | normal | borderline | caseness |
| antidiabetic medication only    | 67     | 21         | 29       |
| antidiabetics+additional medications | 146    | 72         | 93       |
| Total                           | 213    | 93         | 122      |
(Table 3): chi-square calculation between medications and depressive severity:

| Variable                  | depression severity |  | Total |
|---------------------------|---------------------|---|-------|
|                           | normal | borderline | caseness |
| antidiabetic medication only | 64      | 26      | 27     |
| antidiabetics+additional medications | 140     | 102     | 69     |
| Total                     | 204     | 128     | 96     |

Table 4: One way ANOVA calculation of the association between lipid profile and depressive and anxiety severity:

| Variable | Depression : | Normal | Borderline | Caseness | Significance |
|----------|---------------|--------|------------|----------|--------------|
| LDL      | N Mean ± SD   | 204    | 128        | 96       | 0.599        |
|          |               | 109.4±34.2 | 111.2±35.6 | 106±39.9 |              |
| Anxiety :| N Mean ± SD   | 213    | 93         | 122      | 0.076        |
|          |               | 106.2±34.9 | 116.4±34.1 | 109.1±38.5 |              |
| HDL      | N Mean ± SD   | 204    | 128        | 96       | 0.057        |
|          |               | 39.1±12.4 | 35.2±17.7 | 36±18    |              |
| Anxiety :| N Mean ± SD   | 213    | 93         | 122      | 0.000        |
|          |               | 40.3±13.4 | 35.7±20.5 | 33±13.4  |              |
| TG       | N Mean ± SD   | 204    | 128        | 96       | 0.88         |
|          |               | 157.9±84.3 | 153.6±85.4 | 158.1±68.9 |              |
| Anxiety :| N Mean ± SD   | 213    | 93         | 122      | 0.004        |
|          |               | 146.6±76.7 | 152.9±76.9 | 177.1±88.8 |              |
| Cholesterol| N Mean ± SD | 204    | 128        | 96       | 0.036        |
|          |               | 179.8±44.5 | 187.1±49  | 170.9±46.4 |              |
| Anxiety :| N Mean ± SD   | 213    | 93         | 122      | 0.701        |
|          |               | 178.1±43.6 | 182±50.5  | 181.8±48.8 |              |

Table 5: one way ANOVA between lipid profile and depression severity in control group:
| Variable |   | N   | Mean  | Std. Deviation | Sig. |
|----------|---|-----|-------|----------------|------|
| LDL      |   |     |       |                |      |
| normal   | 34| 127.6471 | 5.63475 |
| borderline | 12| 130.1667 | 6.47840 | 0.91 |
| caseness | 4  | 122.7500 | 4.85627 |
| Total    | 50| 127.8600 | 5.97618 |
| HDL      |   |     |       |                |      |
| normal   | 34| 33.6176 | 5.69431 |
| borderline | 12| 31.1667 | 4.72582 | 0.98 |
| caseness | 4  | 38.0000 | 5.41603 |
| Total    | 50| 33.3800 | 5.62389 |
| TG       |   |     |       |                |      |
| normal   | 34| 127.6471 | 5.63475 | 0.91 |
| borderline | 12| 130.1667 | 6.47840 |
| caseness | 4  | 122.7500 | 4.85627 |
| Total    | 50| 127.8600 | 5.97618 |
| cholesterol |   |     |       |                |      |
| normal   | 34| 164.4706 | 9.77391 |
| borderline | 12| 170.3333 | 7.59585 | 0.175 |
| caseness | 4  | 167.0000 | 8.60233 |
| Total    | 50| 166.0800 | 9.38701 |

**Table 6:** one way ANOVA between lipid profile and anxiety severity in control group:
| Variable | N | Mean   | Std. Deviation | Sig. |
|----------|---|--------|----------------|------|
| LDL      |   |        |                |      |
| normal   | 25| 127.520| 5.90282        |      |
| borderline| 18| 129.944| 6.10181        | 0.84 |
| caseness | 7 | 123.714| 3.63842        |      |
| Total    | 50| 127.860| 5.97618        |      |
| HDL      |   |        |                |      |
| normal   | 25| 32.280 | 5.72655        |      |
| borderline| 18| 33.611 | 5.68940        | 0.180|
| caseness | 7 | 36.714 | 4.15188        |      |
| Total    | 50| 33.380 | 5.62389        |      |
| TG       |   |        |                |      |
| normal   | 25| 127.520| 5.90282        |      |
| borderline| 18| 129.944| 6.10181        | 0.93 |
| caseness | 7 | 123.714| 3.63842        |      |
| Total    | 50| 127.860| 5.97618        |      |
| cholesterol |   |        |                |      |
| normal   | 25| 165.600| 10.82051       |      |
| borderline| 18| 167.556| 8.14011        | 0.662|
| caseness | 7 | 164.000| 7.14143        |      |
| Total    | 50| 166.080| 9.38701        |      |

**Supplementary Files**

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