Diabetes-related symptom distress in association with glucose metabolism and co-morbidity: the Hoorn Study

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**Objective:** To determine the associations between diabetes-related symptoms distress, glucose metabolism status, and co-morbidities of type 2 diabetes.

**Research design and methods:** Cross-sectional sample of 281 normal glucose metabolism (NGM), 181 impaired glucose metabolism (IGM) and, 107 subjects with type 2 diabetes mellitus (DM2). We used the Type 2 Diabetes Symptom Checklist (DSC-R) to assess diabetes-related symptom distress.

**Results:** Total symptom distress score (range 0-100) was relatively low for DM2 (mean 8.4 ± 9.4) subjects, though significantly different from IGM (mean 6.5 ± 7.1) and NGM (mean 6.1 ± 7.9) (F = 3.1, df = 2, P = 0.046). Ischemic heart disease was associated with elevated DSC-R scores on three subscales, while depression showed higher symptom distress levels across all DSC-R domains.

**Conclusion:** Worsening glucose metabolism is associated with increasing diabetes-related symptom distress. This relationship is attenuated by ischemic heart disease and particularly by depression.
Type 2 diabetes (DM2) can seriously affect patients’ health-related quality of life (HRQOL) and symptom distress has been recognized as an important patient-reported outcome. So far, empirical data about symptom distress in relation to glucose metabolism status and co-morbidities is sparse, especially among subjects with impaired glucose metabolism (IGM) (pre-diabetes).

Therefore, we analyzed cross-sectional data of the 2000-2001 follow-up examination from the Hoorn Study, a population-based cohort study, to compare levels of diabetes-related symptoms distress among groups of different glucose metabolism status (i.e., NGM, IGM and DM2) and examine the moderating effect of complications and co-morbidities, including depression.

**RESEARCH DESIGN AND METHODS**

The total study sample consisted of 569 subjects, 280 men and 289 women, with a mean age of 69.8 years (SD = 6.4). Details of the 2000-2001 follow-up examination from the Hoorn Study have been described before. All subjects gave written informed consent. Information about age and sex was assessed by means of a questionnaire. BMI and blood pressure were measured using standard methods. Hypertension was defined as a diastolic blood pressure ≥ 90 mmHg, and/or a systolic blood pressure ≥ 140 mmHg, and/or taking antihypertensive medication. Glucose metabolism status was based on an OGTT using the WHO 1999 diagnostic criteria. Ischemic heart disease was determined from the 12-lead electrocardiogram. Prevalent cardiovascular disease was assessed by the Rose questionnaire.

Neuropathy was defined as the presence of impaired foot sensitivity, assessed with Semmes-Weinstein monofilaments. Diabetic retinopathy was defined as Wisconsin-grade 1.5 or higher, based on retinal photography. Microalbuminuria was defined as an albumin-to-creatinine ratio of > 2.0 mg/mmol. Depression was assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D score ≥ 16). Diabetes-related symptom distress was measured with the revised version of the Type 2 Diabetes Symptom Checklist (DSC-R).

Chi-square tests (%) and ANOVA’s were performed to study differences in characteristics, co-morbidities and DSC-R variables for NGM, IGM and DM2. Since, previous studies suggest that depression is associated with increased levels of symptom distress, we included depression as a covariate in the ANOVA to sort out the potential interaction between the DSC-R total scores and, NGM, IGM and DM2. Mann-Whitney U tests were performed for between-group comparisons regarding DSC-R, i.e. (a) DM2 vs. IGM and (b) DM2 vs. NGM. Student’s t-tests were used to determine the association between co-morbidities and DSC-R scores in subjects with and without co-morbidity. P < 0.05 was considered statistical significant. All analyses were performed using SPSS, version 11.5, for Microsoft Windows.

**RESULTS**

ANOVA’s showed that worsening glucose metabolism, represented by NGM (mean 6.1 ± 7.9), IGM (mean 6.5 ± 7.1) and DM2 (mean 8.4 ± 9.4), was associated with increasing DSC-R total scores (F = 3.1, df = 2, P = 0.046). Additionally, we included depression (CES-D score) as a covariate in the ANOVA to sort out the potential interaction. Virtually the same mean DSC-R scores for the NGM (6.0 ± 7.7), IGM (mean 6.1± 7.0) and DM2 (mean 8.5 ± 9.7) were found, though not statistically significant (F = 0.99, df = 2, P = 0.245). Mann-Whitney U tests revealed that DM2 patients reported
significantly greater burden of neuropathic pain ($P = 0.033$), sensibility symptoms ($P = 0.004$), and total symptom distress ($P = 0.005$) compared to subjects with NGM, but not compared to those with IGM (See Table A1 in the Online Appendix available at http://care.diabetesjournals.org).

Subjects with ischemic heart disease had a significantly higher total DSC-R score compared with non-ischemic heart disease subjects. Most strikingly, both the DSC-R total and all sub-scale scores appeared about three-fold higher for subjects with depression (CES-D score $\geq 16$) compared to those without depression, at all three stages of glucose metabolism (Table 1).

CONCLUSION

This is the first study to demonstrate the association between glucose metabolism status and the level of diabetes-related symptom distress, using the DSC-R. Worsening glucose metabolism is associated with increasing diabetes-related symptom distress. This relationship is attenuated by ischemic heart disease and by depression in particular. The results presented provide supportive evidence of the validity and reliability of the revised Diabetes Symptom Checklist.

The fact that subjects with depression reported significantly higher DSC-R levels compared to those without depression suggests that negative affect has a strong amplifying effect on diabetes symptom burden, representing higher illness intrusiveness. The association between diabetes symptoms and depressive mood could also be bi-directional, with diabetes symptoms contributing to the development of depressive symptoms. Yet, even after correction for depression we found that diabetic subjects report higher levels of diabetes symptom distress than subjects with NGM or IGM, underscoring the importance of glucose metabolism status.

In persons screened for type 2 diabetes, relatively high levels of symptom distress may flag a co-morbid depression and a need for antidepressant treatment. Likewise, in patients with established diabetes, high symptom distress despite relatively good glycemic control may point at elevated levels of depression. New longitudinal research on this complex relationship is warranted to further understand underlying mechanisms and to develop effective therapeutic strategies.

The strengths of our study are that we used data from a population-based sample, gold standard measurement to determine glucose metabolism status (i.e. OGTT), the availability of information on co-morbidities and the use of the validated DSC-R to determine diabetes-related symptom distress. There are also limitations. This present study has a cross-sectional design. Further prospective research should help to clarify the course of symptom distress over time across different stages of glucose metabolism. Next, determining the impact of different treatment strategies (i.e. diet, blood glucose lowering drugs, insulin) on the DSC-R levels among diabetes patients was beyond the scope of this study. However, given the increasing importance of patient reported outcomes, future studies should carefully explore the impact of diabetes medication on symptom distress as a measure of HRQoL.
REFERENCES


Table 1. Mean scores for diabetes-related symptom distress total and subscale scores in subjects with and without co-morbidity among all participants.

<table>
<thead>
<tr>
<th>Co-morbidity*</th>
<th>Ischemic heart disease†</th>
<th>Prevalent cardiovascular disease‡</th>
<th>Neuropathy</th>
<th>Retinopathy</th>
<th>Microalbuminuria</th>
<th>Depression</th>
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<tbody>
<tr>
<td></td>
<td>DSC-R (0-100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No n=345</td>
<td>Yes n=202</td>
<td>No n=465</td>
<td>Yes n=100</td>
<td>No n=215</td>
<td>Yes n=203</td>
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<tr>
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<td>8.1</td>
<td>7.1</td>
<td>6.6</td>
<td>5.7</td>
<td>8.4†</td>
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<tr>
<td>Hypoglycemic</td>
<td>5.1</td>
<td>5.3</td>
<td>5.3</td>
<td>5.3</td>
<td>4.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>4.2</td>
<td>7.0‡</td>
<td>5.4</td>
<td>4.7</td>
<td>4.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Sensibility</td>
<td>4.7</td>
<td>5.8</td>
<td>5.0</td>
<td>5.4</td>
<td>4.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11.5</td>
<td>14.1</td>
<td>13.1</td>
<td>11.1</td>
<td>10.9</td>
<td>12.6</td>
</tr>
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<td>Cognitive distress</td>
<td>6.2</td>
<td>8.6‡</td>
<td>7.3</td>
<td>7.3</td>
<td>6.1</td>
<td>7.9</td>
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<tr>
<td>Cardiovascular</td>
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<td>6.7</td>
<td>6.0</td>
<td>6.5</td>
<td>5.4</td>
<td>5.8</td>
</tr>
<tr>
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<td>6.6‡</td>
<td>5.3</td>
<td>6.2</td>
<td>5.5</td>
<td>5.3</td>
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<td>DSC-R total score</td>
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<td>7.7‡</td>
<td>6.7</td>
<td>6.6</td>
<td>5.7</td>
<td>6.9</td>
</tr>
</tbody>
</table>

* Numbers do not total exactly due to missing values, particular for retinopathy.
‡ P < 0.01; † P < 0.05
† Based on electrocardiogram-recording.
‡ Assessed by the Rose questionnaire.