

Apathy in older patients with type 2 diabetes

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Abstract

Objectives: To determine the prevalence, incidence, persistence, likely causes and consequences of apathy in patients with type 2 diabetes and to compare the prevalence with a healthy control sample.

Design: Cross-sectional comparison of diabetic and control samples; longitudinal follow-up of diabetic sample.

Setting: Academic research department.

Participants: Non-demented, older patients with long-standing type 2 diabetes (n=122) recruited from a community-based cohort study and 69 healthy volunteers.

Measurements: Clinical assessments of apathy and potential causative conditions, repeated in the diabetic sample after 16.7±2.5 months. Informant rated symptoms from the 14-item Apathy Scale were used to generate apathy diagnoses based on standardised criteria.

Cognition was assessed by Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR).

Results: The diabetic and control samples had the same age and MMSE scores, but the diabetic sample had a higher frequency of depression, cerebrovascular history and cognitive deficits. Apathy was more prevalent in diabetes (diabetic vs control sample: 13.9 vs 1.4%, $P=0.005$) and was independently associated with CDR 0.5 status (odds ratio (95% CI): 3.66 (1.25-19.70), $P=0.018$) and depression (8.48 (2.74-26.21), $P<0.001$). In 108 diabetic patients who were followed up, incident apathy occurred in 7.4% of cases, and persisted in 50% of those with baseline apathy. Baseline apathy was independently associated with $\ln\text{HbA}_{1c}$ levels (Beta 0.20, $P=0.024$) and incident/persistent apathy was associated with greater risk of cognitive decline (6.72 (1.19-37.87), $P=0.031$).

Conclusions: Apathy is a frequent neuropsychiatric syndrome in older patients with type 2 diabetes, and is associated with poor glycaemic control and cognitive decline.

Objective

Apathy is defined as a lack of motivation, evidenced by diminished goal-directed behaviour, cognition or emotion relative to previous functioning (1). Apathy is a common neuropsychiatric symptom that complicates many age-related disorders including Alzheimer's disease, Parkinson's disease and stroke (2, 3) and is associated with adverse health consequences (2, 4, 5). The symptoms of apathy frequently overlap with depression but apathy is a syndrome distinct from clinical depression (6). The adverse consequences of apathy that have been documented include decreased recovery following stroke and increased caregiver stress in dementia caregivers (2). In Alzheimer's disease, apathy is a significant predictor of cognitive and functional decline, depression and parkinsonism (4).

Apathy may also be common in older populations (7, 8) where associations with stroke, depression and cardiovascular risk factors including diabetes have been reported (8, 9). There have been few studies in diabetes but a recent study from a clinic population reported that 50 out of 81 older diabetic patients had apathy, which was associated with reduced adherence to self-management behaviours, obesity and a non-significantly increased HbA_{1c} level (10). The authors subsequently reported that methylphenidate treatment improved glycaemic control in 8 apathetic diabetic patients with Alzheimer's disease (11). The aims of the present study were to investigate the prevalence, incidence, persistence and associates of apathy in a sample of older subjects with type 2 diabetes and to compare prevalence rates with a healthy non-diabetic control sample.

Methods

Patients with diabetes: The diabetic sample was recruited from type 2 participants in an ongoing, observational study of known diabetes, the Fremantle Diabetes Study, Phase II (FDS2). The sample was purposively recruited to a longitudinal study where inclusion criteria were age ≥ 65 years, long duration diabetes (≥ 10 years), absence of dementia and adequate linguistic/educational ability to undergo a cognitive assessment. The present study sample comprised all recruited patients who also had a suitable informant to complete an apathy assessment. Exclusion criteria included severe organ dysfunction, malignancy, neurological/psychiatric diagnoses and conditions that precluded participation in magnetic resonance imaging. FDS2 recruited patients between 2008 and 2011 and details of recruitment procedures including classification of diabetes type have been previously published (12).

Healthy controls: Volunteers were recruited from the same geographic area to a cognition/neuroimaging study using local advertising and approaching partners of patients attending local geriatric clinics. Inclusion and exclusion criteria were similar to those described above except for the presence of diabetes. The study protocols were approved by the Human Research Ethics Committee of the Southern Metropolitan Area Health Service and all participants gave informed consent.

Assessments

Both samples underwent identical assessments of apathy and cognitive function whilst the methods used to assess cerebrovascular disease and depression differed. The diabetic patients had repeat assessments of apathy, cognition, cerebrovascular disease and depression after approximately 18 months whilst the control sample was assessed once only. Apathy was assessed by a suitable informant using the 14-item Apathy Scale (13, 14), and the data were

used to generate diagnostic criteria for apathy as described in a previous publication (15, 16). Cognition was assessed using the Mini-Mental State Examination (MMSE), and the Clinical Dementia Rating (CDR) scale where the researcher uses data from both participant and informant to rate six domains – memory, orientation, judgement/problem solving, community affairs, function at home/hobbies, personal care (17). This generates CDR ratings from normal cognition (CDR 0) to severity levels of dementia (CDR 1-3) and an intermediate category (CDR 0.5) defines mild cognitive impairment. The inclusion criteria for both samples in the study permitted individuals with CDR 0.5 given their unclear status regarding the presence of dementia. Depression was assessed in the diabetic sample using the 9-item Patient Health Questionnaire (PHQ-9) that has been validated in diabetes (18). The PHQ-9 provides a depression score and the responses can be used to generate DSM5 depression diagnoses (major and minor depression). In the control sample, depression was assessed using the Mini International Neuropsychiatric Interview, a structured psychiatric diagnostic interview. In the diabetic sample, a history of stroke or transient ischaemic attack (TIA) was assessed using the 8-item Questionnaire for Verifying Stroke-Free Status (QVSS) (19) whilst in the control sample, stroke/TIA history was obtained based on ratings on the Cumulative Illness Rating Scale, medical interview and case note review. Instrumental activities of daily living (IADL) were assessed using the Lawton scale (20). Additional diabetes-related data were collected during the FDS2 assessment supplemented and/or updated at baseline and at follow up.

Statistical analysis

The computer package IBM SPSS Statistics 19 (IBM Corporation, Armonk, New York, United States) was used for statistical analysis. Data are presented as proportions, mean \pm SD, geometric mean (SD range), or, in the case of variables which did not conform to a normal or

log-normal distribution, median [inter-quartile range, IQR]. For independent samples, two-way comparisons for proportions were by Fisher's exact test, for normally distributed variables by Student's *t*-test, and for non-normally distributed variables by Mann-Whitney U-test and Kruskal-Wallis test. Multiple logistic regression analysis used forward conditional modelling and linear regression analysis used stepwise modelling ($p < 0.05$ for entry and > 0.10 for removal in both).

Results

The clinical characteristics of the diabetic and non-diabetic samples are displayed in table 1. They had a similar age and MMSE scores but the diabetic sample had fewer females and a higher frequency of depression, history of TIA/stroke and CDR rating of 0.5. The diabetic sample had long duration diabetes (mean 21.2 ± 4.9 years), 5.9 % were controlled with diet alone, 51.2% with oral hypoglycaemic agents alone and 42.9% were taking insulin usually in combination with oral agents. Both samples were community-dwelling and independent in basic and most instrumental ADL. Apathy Scale scores were significantly higher and apathy was significantly more prevalent in the diabetic sample compared to the healthy control group (13.9% vs 1.4%, $P = 0.005$). Using logistic regression with the entire sample and after adjusting for age, gender, CDR status, depression status (major or minor compared with no depression) and history of stroke/TIA in the model, apathy was independently associated with CDR 0.5 rating (odds ratio (95% CI): 3.66 (1.25-10.70), $P = 0.018$) and depression (8.48 (2.74-26.21), $P < 0.001$).

Apathy in type 2 diabetes: Baseline and follow-up findings

Baseline associations with apathy in the diabetic sample are displayed in table 2. Apathy was significantly associated with CDR status, depression and higher HbA_{1c} levels with no

differences in obesity, diabetes duration or in intensity of glucose-lowering therapy. In a linear regression model, that included age, gender, apathy, CDR status and depression as explanatory variables, apathy was independently associated with $\ln\text{HBA}_{1c}$ (Beta 0.20, $P=0.024$).

After 16.7 ± 2.5 months, 108 diabetic participants underwent repeat apathy assessment (there were 2 deaths, 10 withdrawals and in 2 the informant was unavailable). At follow up, there were 8 new cases of apathy, 7 cases where apathy persisted, 7 cases where apathy recovered and 86 cases without apathy at both assessments giving a follow up prevalence and incidence of 13.9% and 7.4% respectively. There were significant baseline differences between those with and without apathy at follow-up (i.e. comparing incident/persistent with never/resolved apathy) with baseline apathy, MMSE scores, CDR status and depression being associated with follow-up apathy (table 3). Multiple logistic modelling was used to explore baseline predictors of follow-up apathy (i.e. persistent/incident apathy). In a model that included age, sex, and depression, only baseline CDR 0.5 rating (3.82 (1.12-13.0), $P=0.033$) and baseline apathy (9.22 (2.44-34.89), $P=0.001$) predicted follow-up apathy. Those with incident/persistent apathy had greater cognitive decline compared with those with never/improved apathy (20.0% vs 4.4% had a decline in CDR rating, chi-square 5.1, $P=0.024$). The association between cognitive decline and incident/persistent apathy remained significant (6.72 (1.19-37.87), $P=0.031$) in a logistic regression model that included baseline depression, CDR status and new-onset depression.

To explore possible explanations for recovered, incident, and persistent apathy, baseline apathy, depression and MMSE scores were examined further. Baseline Apathy Scale scores were significantly different among the four apathy conditions (never, recovered, incident,

persistent: ANOVA $F=31.9$, $P<0.001$). Those with incident apathy had higher baseline Apathy Scale scores than those who never had apathy (18.6 ± 4.9 vs 9.2 ± 4.9 , $P<0.05$, Bonferroni post-hoc test), and those with recovered apathy had lower baseline scores than those with persistent apathy (17.4 ± 2.9 vs 23.6 ± 5.9 , $P<0.05$, Bonferroni post-hoc test). Baseline PHQ-9 scores were also significantly different among the four conditions ($P=0.04$, Kruskal-Wallis test) with lower median depression scores at baseline (that approached statistical significance) in recovered compared with persistent apathy (2 [2-4] vs 13 [7-16], $P=0.053$). There were no differences in MMSE scores.

Conclusions

In the present study, we investigated the prevalence, incidence and persistence of apathy in a sample of non-demented, older patients with long-standing type 2 diabetes using diagnostic criteria proposed for neurodegenerative and psychiatric disorders (15, 16). Apathy was present in almost 14% of the diabetic cases, much higher than seen in a healthy control sample. After almost 18 months follow-up, another 7% of the sample developed incident apathy and approximately half of those with baseline apathy at baseline remained apathetic and half recovered. Apathy was associated with a clinically relevant elevation in HbA_{1c} levels in the diabetic sample fulfilling the additional apathy criterion of evidence for impairment in an important area of functioning (16) given that glycaemic control is strongly associated with self-motivation (21). We conclude that apathy is an important neuropsychiatric syndrome in older patients with type 2 diabetes that is likely to be a barrier to effective self-management.

Several potential causes of apathy were investigated. Both depression and cognitive impairment were associated with apathy in the combined sample and cognitive impairment

predicted incident apathy in the diabetic sample. There was no evidence for a role for cerebrovascular disease although subclinical cerebrovascular disease, common in type 2 diabetes, was not excluded. Notably, the degree of cognitive impairment was mild in this study sample; all were living independently, MMSE scores were within the normal range and the CDR 0.5 rating denotes very mild impairment (17). Published prevalence rates for apathy vary widely in part because of the different methods used to define the syndrome (4) and such methodological differences may explain the previously reported high frequency of apathy in type 2 diabetes (10). We used a valid instrument to rate the symptoms, a valid algorithm to classify the symptoms into specific domains and applied standardised diagnostic criteria for apathy. Prevalence rates for apathy using diagnostic criteria of 43% for Mild Cognitive Impairment and from 21-55% for mild Alzheimer's Disease in clinic-based samples have been recently published (16, 22, 23). The present study prevalence of 14% in diabetes is lower but possibly consistent with the mild degree of cognitive impairment.

Relatively few longitudinal studies have been conducted to assess the persistence of apathy. The available data indicate that apathy generally persists in progressive neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease (23, 24) but is more likely to recover when associated with cerebrovascular disease, where between 44 and 67% of apathy resolves at follow-up (25). In our study, apathy persisted or recovered in equal proportions and differences in baseline Apathy Scale scores and the PHQ-9 suggest possible reasons. Persistent apathy was associated with higher scores on the Apathy Scale and PHQ-9 than recovered apathy indicating that recovery is associated with less severe apathy and less depression. In addition, incident apathy was associated with higher baseline Apathy Scale scores than in those who never had apathy indicating that incident apathy occurred in individuals already on a trajectory of increasing apathy. Future studies with larger sample

sizes are required to confirm these findings but the relatively high recovery rate in diabetes may point to a cerebrovascular mechanism in diabetes-associated apathy.

In our study, persistent and incident apathy predicted cognitive decline. This finding is consistent with previous studies demonstrating that apathy is associated with an increased risk of progression from predementia states to dementia (26, 27). Type 2 diabetes is a known risk factor for dementia and various predementia states and is also associated with an accelerated conversion to dementia from predementia (28-30). Consequently, apathy may be a useful clinical predictor of cognitive impairment that is more likely to progress in type 2 diabetes. The presence of apathy in type 2 diabetes is likely to have other clinical consequences. Apathy has an adverse impact on personal quality of life (31), and would be expected to have adverse effects on the spouse or supporting family because of the need to assume more of the burden of managing the complex care commonly employed to control diabetes. Undetected apathy is likely to thwart the efforts of diabetes clinical staff who may attempt to deploy fruitless educational or motivational strategies or increase the complexity of diabetes treatment regimes. It is also possible that at least some of the depression reported in diabetes may be due to diagnostic overlap with apathy.

The present study has a number of strengths. These include the longitudinal assessment of apathy using standardised diagnostic criteria, the representative nature of the diabetic cohort from where the sample was drawn, and the detailed nature of the clinical assessments including the use of a validated instruments and information from informants. The major limitations are the small sample sizes and the known biases associated with selecting volunteer controls (recruitment bias) and participants from an ongoing cohort study (recruitment and survival bias). The representativeness of the findings are further limited

given that we only studied non-demented participants, with long duration diabetes who were free of medical implants commonly used in patients with vascular disorders.

In summary, apathy was common in a sample of older people with long-standing type 2 diabetes and was associated with worse glycaemic control and cognitive decline. Apathy is an important neuropsychiatric symptom in type 2 diabetes that is likely to have clinical implications for patients and their families.

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Table 1: Cross-sectional associations between patients with type 2 diabetes and a healthy control group.

	Controls N=69	Diabetes N=122	P-value
Age (years)	74.6±7.0	73.5±7.0	0.31
Gender (% female)	66.7	32.0	<0.001
MMSE score (median [IQR])	29 [27.5-30]	29 [28-30]	0.93
Clinical Dementia Rating 0.5 (n, %)	6 (8.7%)	35 (28.7%)	0.001
Any depression (n, %)	3 (4.3%)	18 (14.9%)	0.026
Major depression (n, %)	0 (0%)	8 (6.6%)	0.03
History of stroke/TIA (n, %)	0 (0%)	29 (23.8%)	<0.001
Apathy scale score	2.9±3.4	11.6±6.6	<0.001
Apathy by criteria (n, %)	1 (1.4%)	17 (13.9%)	0.005

Table 2: Baseline associations with apathy in 122 patients with type 2 diabetes.

	No apathy N=105	Apathy N=17	P-value
Age (years)	73.80±7.1	71.7±6.7	0.26
Gender (% female)	32.4	29.4	0.81
Duration of diabetes (years)	20.0 [17.5-23.2]	19.2 [17.6-24.5]	0.94
Body mass index (kg/m ²)	29.2±5.1	27.8±0.3	0.28
Therapy (% diet/oral agents/insulin)	6.8/52.4/40.8	0.0/43.8/56.3	0.36
HbA _{1c} concentration (%)	7.2 [6.5-7.9]	7.7 [7.2-8.8]	0.026
MMSE score (median [IQR])	29 [28-30]	29 [27-29.5]	0.63
Clinical Dementia Rating 0.5 (%)	24.8	52.9	0.017
Any depression (%)	9.6	47.1	<0.001
Major depression (%)	3.8	23.5	0.002
History of stroke/TIA (%)	26.7	5.9	0.06
Apathy scale score	9.9±5.4	20.9±5.2	<0.001

Table 3: Associations between baseline variables and persistent/incident apathy in 108 patients with type 2 diabetes who were re-assessed after a mean 16.7 months.

Baseline variables	No apathy at follow-up N=93	Apathy at follow-up N=15	P-value
Age	73.6±6.8	73.0±6.8	0.72
Gender (% female)	32.3	26.7	0.67
Apathy (%)	7.5	46.7	<0.001
MMSE score (median [IQR])	29 [28-30]	28 [25-29]	0.012
Clinical Dementia Rating 0.5 (%)	24.7	60.0	0.006
Any depression (%)	12.9	33.3	0.044
Major depression (%)	6.5	20.0	0.08

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