Characteristics of an Adult Population With Newly Diagnosed Type 2 Diabetes

The relation of obesity and age of onset

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OBJECTIVE — To determine whether adults diagnosed with type 2 diabetes at 18–44 years of age (early type 2 diabetes) have different metabolic profiles at diagnosis than adults diagnosed at ≥45 years of age (usual type 2 diabetes).

RESEARCH DESIGN AND METHODS — Within a health maintenance organization, we studied characteristics among 2,437 adults newly diagnosed with type 2 diabetes between 1996 and 1998 who had measured weight, HbA_{1c}, blood pressure, and cholesterol within 3 months of diagnosis. We abstracted clinical data from electronic medical records. We compared mean and proportional differences with parametric t tests and χ^2 analyses, respectively. We used multiple logistic regression to identify the factors independently associated with the onset group (early vs. usual type 2 diabetes).

RESULTS — There was an inverse linear relationship between BMI and age at diagnosis of type 2 diabetes ($P < 0.001$). On univariate analysis, adults with early type 2 diabetes were more obese (BMI 39 vs. 33 kg/m^2, $P < 0.001$), were more likely to be female ($P = 0.04$), had slightly worse glycemic control (HbA_{1c} 7.7 vs. 7.5%, $P = 0.03$), had a higher prevalence of diastolic hypertension (37 vs. 26%, $P < 0.001$), despite a lower prevalence of systolic hypertension (34 vs. 55%, $P < 0.001$), and had an equally high rate of abnormal lipids (82 vs. 78%, $P = 0.13$) than adults with usual type 2 diabetes. BMI, female gender, cholesterol, and diastolic and systolic blood pressure remained independently associated with onset group at multivariate analysis.

CONCLUSIONS — Although both onset groups were on average obese, the inverse linear relationship of obesity and age of diabetes onset that we observed suggests that obesity is a continuous risk rather than a threshold risk for diabetes onset. Both onset groups had a high prevalence of cardiovascular disease risk factors.

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T ype 2 diabetes is now an epidemic in the U.S. (1,2). The estimated prevalence of diagnosed diabetes in the U.S. increased from 0.37% in 1935 (3) to 5.1% in 1988–1994 (1) and jumped to 6.9% by 1999 (4). Obesity increased by 70% in adults 18–29 years of age, and type 2 diabetes increased by 70% in adults 30–39 years of age over the last decade, making young adults the fastest growing group for both obesity and type 2

diabetes (5,6). Despite this rapid change in demographics, little is known about these young adults who are increasingly developing type 2 diabetes.

To our knowledge, no study has evaluated baseline metabolic profiles in a population newly diagnosed with type 2 diabetes or how these profiles may differ depending on age at onset. The purpose of the present study was to determine whether metabolic profiles are different at

diagnosis in adults with early onset compared with usual onset type 2 diabetes in a population of adults with incident type 2 diabetes.

RESEARCH DESIGN AND METHODS

Research setting and study population

The subjects of this study were members of a long-established, not-for-profit, group-model health maintenance organization, Kaiser Permanente Northwest Division (KPNW). KPNW provides comprehensive, prepaid coverage to ~20% of the Portland, Oregon, population (~420,000 people). Subscriber demographics are similar to the area population as a whole: ~90% are non-Hispanic white, and 10% comprise of African-American, Asian/Pacific Islander, Native American, and people of Hispanic descent (7,8). A total of 18.5% of KPNW's members are eligible for Medicare (>64 years of age), and ~8% are covered under Medicaid through a contract with the Oregon Health Plan to provide medical coverage for Oregon residents below the poverty level (9).

All members of KPNW have access to medically necessary clinical services by or on referral from their personal primary care physician. The organization maintains administrative and clinical electronic databases containing information on inpatient admissions, pharmacy dispenses, outpatient visits, laboratory tests, and outside claims and referrals. All of these databases are linked through a unique health record number given to each member at the time of his or her first enrollment into the health plan.

The KPNW Diabetes Registry contains a continuous census of >30,000 KPNW members with diagnosed diabetes since 1 January 1987. The methods used to create the diabetes registry are described elsewhere (10). Validation studies have shown the registry to be >99% sen-

sitive and 99% specific for diagnosed diabetes.

The following inclusion criteria were used for the present study population ($n = 2,437$): any KPNW member newly diagnosed with type 2 diabetes between 1996 and 1998 who also had measured weight, HbA_{1c}, blood pressure, and lipids within 3 months of diagnosis. To ensure that the subjects were newly diagnosed (incident), a patient had to have at least one full year of health-plan membership before the date of diagnosis.

We defined type 2 diabetes as no purchase of insulin in the first year after diabetes diagnosis. We can reasonably estimate insulin use, because ~97% of our health maintenance organization members receive all or most of their insulin from our pharmacies (based on a survey of 11,331 KPNW members with diabetes, 58.5% of respondents) (11).

Age at diagnosis was calculated using the date of entry into the diabetes registry. Subjects were classified as "early onset" if they were diagnosed before age 45 (early type 2 diabetes) and were considered "usual onset" if they were diagnosed at or after 45 years of age (usual type 2 diabetes). We chose 45 years as the definition of usual onset, as virtually all adults diagnosed at >45 years of age have type 2 diabetes (3). Nationally >90% of people with type 2 diabetes are >45 years of age (12). Similarly, ~90% of our adult population was diagnosed at >45 years of age.

Measurement of subject characteristics

We reviewed the outpatient electronic medical record to ascertain height, weight, and blood pressure measured at each individual's clinic visits, and we used the laboratory results database to ascertain HbA_{1c} and lipid measurements within 3 months of diagnosis. If more than one measurement was available in the medical record, we used the measurement at diagnosis, or if that was not available, the measurement closest to the date of diagnosis. During the study period, KPNW measured long-term glucose control using two tests: HbA_{1c} and fructosamine. HbA_{1c} was more commonly used. To facilitate analysis, we converted fructosamine results (bG21 colorimetric assay; Boehringer Mannheim, Indianapolis, IN) to the HbA_{1c} equivalent (Diamat HPLC assay; Bio-Rad, Hercules, CA) us-

ing the following formula: fructosamine/ $40 = HbA_{1c}$. This formula closely approximates the actual relation observed within the health maintenance organization based on regression analysis of 364 paired samples drawn simultaneously ($R^2 = 0.65$, $P < 0.001$ [S. Welch, unpublished data] (11).

Hypertension was defined as an outpatient-measured systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg (13). A person was classified as having abnormal lipids if he/she had any of the following characteristics: total cholesterol >200 mg/dl, LDL cholesterol >130 mg/dl, HDL cholesterol <36 mg/dl, or fasting triglycerides >250 mg/dl (14).

Subjects were classified as being depressed if they had a clinical diagnosis of depression or dysthymia (ICD-9 CM codes 296.2, 296.3, 298.0, 300.4, 309.1, and 311.0) or if they received antidepressant medications before the diagnosis of diabetes. To ensure that the antidepressants were dispensed for depression and not for some other medical reason (e.g., peripheral neuropathy), we required that the average daily dose of all such dispenses be equal to at least 100% of the minimum therapeutic dose as defined by the Agency for Health Care Policy and Research Clinical Practice Guidelines for the treatment of depression (15,16).

BMI, calculated as kilograms per meter squared, was based on the weight within 3 months of diagnosis and any recorded height since age 18. Nearly 60% of individuals do not have a height recorded in their electronic medical record. For these individuals, we used their self-reported height from the 1997 KPNW Diabetes Survey (11).

Statistical analyses

We conducted all statistical analyses using the SAS Statistical Analysis System version 6.12 (SAS Institute, Cary, NC). We used χ^2 tests for comparing proportions and t tests for comparing mean differences. Multiple logistic regression was used to identify factors that were independently associated with early onset type 2 diabetes. Random glucose was excluded from the multiple logistic regression analyses, as fewer than half of the study subjects had a random glucose at diagnosis. Before the final multiple regression, subsets of variables describing blood pressure and cholesterol were examined in detail

to determine which combinations of these variables would result in the best overall model and still avoid multicollinearity problems. Dichotomous categories of blood pressure (e.g., systolic >130 mmHg) were found to be poorer correlates of early onset type 2 diabetes and were excluded from the final model. Similarly, within the cholesterol group of variables, the "any abnormal lipids" variable was excluded from further analyses.

Adjusted odds ratios (ORs) were obtained from logistic regression analyses. Confidence intervals for the ORs were based on the asymptotic normality of the parameter estimates (17). All of the statistical tests that we report were two-sided, and the term "statistically significant" implies $P < 0.05$. To allow the reader to more easily interpret the univariate results, we did not adjust for multiple comparisons. Therefore, P values should be interpreted with caution in these analyses.

RESULTS — A total of 2,437 individuals met the inclusion criteria (277 early onset and 2,160 usual onset) and comprise the study population. The study population did not represent a healthier subset of the entire KPNW incident cohort of 6,109 people diagnosed with type 2 diabetes during the same time period, as both had a similar distribution of age at diabetes diagnosis, gender, HbA_{1c}, and blood pressure at diagnosis (data not shown). For the entire study population, the average glycemic control at diagnosis was $7.5 \pm 1.6\%$.

Univariate analysis

The average BMI was significantly higher for early type 2 diabetes than for usual type 2 diabetes (39 vs. 33 kg/m², $P < 0.001$, Table 1). Furthermore, there was a strong inverse linear relation between BMI and age at diagnosis (Fig. 1). Average BMI decreased from 38.3 kg/m² in the youngest age group to 28.8 kg/m² in the oldest age group (Fig. 1, $P < 0.0001$ for trend).

A total of 51% of the early onset group were female compared with 44% of the usual onset group. HbA_{1c} was slightly higher in the early onset group (7.7 vs. 7.5%, $P = 0.034$). In addition, among the 1,275 people who had random glucose values measured within 3 months of diagnosis, random glucose values were higher among early type 2 diabetes than among usual type 2 diabetes (261 vs. 216

Table 1—*Comparison of characteristics at diagnosis with early and usual type 2 diabetes*

	Early type 2 diabetes	Usual type 2 diabetes	P
n	277	2,160	
BMI (kg/m^2)	39 ± 24	33 ± 27	<0.001
Gender (female %)	51	44	0.035
HbA$_{1c}$ (%)	7.7 ± 1.8	7.5 ± 1.6	0.034
Random glucose (mg/dl)*	261 ± 127	216 ± 113	<0.001
Systolic blood pressure (mmHg)	127 ± 16	135 ± 18	<0.001
Systolic blood pressure >130 mmHg	34	55	<0.001
Diastolic blood pressure (mmHg)	82 ± 10	79 ± 10	<0.001
Diastolic blood pressure >85 mmHg	37	26	<0.001
Hypertension†	49	61	<0.001
Total cholesterol (mg/dl)	205 ± 43	205 ± 49	0.933
HDL cholesterol (mg/dl)	33 ± 15	37 ± 16	<0.001
LDL cholesterol (mg/dl)	77 ± 58	91 ± 52	<0.001
Triglycerides (mg/dl)	241 ± 182	231 ± 201	0.414
Cholesterol-to-HDL ratio	8.1 ± 4.8	7.0 ± 4.6	<0.001
Abnormal lipids‡	82	78	0.126
Depression (%)	21	16	0.040

Data are means ± SD and %. *Based on 155 younger-onset and 1,120 usual-onset subjects who received a random glucose test within 3 months of diagnosis; †hypertension is defined as systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg; ‡abnormal lipids are defined as total cholesterol >200 mg/dl, LDL cholesterol >130 mg/dl, triglycerides >250 mg/dl, or HDL cholesterol <36 mg/dl.

mg/dl, $P < 0.001$). Although the prevalence of hypertension was higher with usual type 2 diabetes (61%), 49% of those with early type 2 diabetes had hypertension. Furthermore, diastolic hypertension was nearly 1.5 times more prevalent in those with early type 2 diabetes compared with usual type 2 diabetes (37 vs. 26%, $P < 0.001$)

The majority of people with early type 2 diabetes had abnormal lipids, although this was not statistically higher than in usual type 2 diabetes (82 vs. 78%). Mean total cholesterol level was similar for each of the groups; however, the average HDL and LDL cholesterol levels were markedly different. The early onset group surprisingly had lower average HDL cholesterol levels than the usual-onset group (33 vs. 37 mg/dl, $P < 0.001$), despite similar triglyceride levels. As would be expected with younger age, the LDL cholesterol level was lower in the early onset group compared with the usual-onset group (77 vs. 91 mg/dl, $P < 0.001$). The total cholesterol–to–HDL cholesterol ratio was much higher in the early onset group (8.1 vs. 7.0, $P < 0.001$).

Multivariate analysis
Because many of the characteristics may be related to the age at which diabetes was diagnosed, we performed multiple logistic regression to simultaneously assess the independent associations of these variables with early or usual type 2 diabetes. The variables in the multivariate model included BMI, female gender, HbA$_{1c}$, systolic and diastolic blood pressure, hypertension, total cholesterol, LDL and HDL cholesterol, triglycerides, total cholesterol–to–HDL cholesterol ratio, and depression. After adjusting for all other variables, the odds of early type 2 diabetes increased by 6% for each 1 kg/m^2 increase in BMI (OR 1.06, 95% CI 1.05–1.08). Other variables that were significantly and independently associated with early type 2 diabetes include female gender (1.36, 1.01–1.83), systolic blood pressure (per 10 mmHg: 0.57, 0.50–0.65), diastolic blood pressure (per 5 mmHg: 1.39, 1.26–1.53), total cholesterol (per 20 mg/dl: 1.14, 1.01–1.30), HDL cholesterol (per 5 mg/dl: 0.83, 0.74–0.94), LDL cholesterol (per 10 mg/dl: 0.94, 0.90–0.99), and total cholesterol–to–HDL cholesterol ratio (0.90, 0.81–0.99). HbA$_{1c}$, triglycerides, depression, and the dichotomous variable for hypertension (>130/85 mmHg) were not independently associated with type 2 diabetes onset group.

Defining hypertension and hyperlipidemia in the model based on drug treatment or on physician diagnosis rather than on measured levels did not change the direction or overall significance of the

results (data not shown). There was also no significant interaction between measured hypertension value and diagnosis of hypertension, and the same was true for measured lipid levels and hypercholesterolemia diagnosis.

Univariate and multivariate analyses stratified by gender
To determine whether there were gender differences within and between onset groups, analyses were stratified by gender. Interestingly, only the early onset male subjects had greater diastolic blood pressures, accounting for the effect that was seen in the entire early onset group. A total of 43% of the early onset males had diastolic hypertension compared with 26% of the older-onset males ($P < 0.001$). Young men had an equally high prevalence of hypertension (59%) as adult men with usual onset type 2 diabetes. Similarly, average glycemic control was much worse at diagnosis among young men with early onset than among men with later onset (8.0 vs. 7.5%, $P < 0.01$). On multivariate analysis, higher BMI, higher diastolic blood pressure, and lower systolic blood pressure remained independent correlates of early onset type 2 diabetes for both men and women.

CONCLUSIONS — In this population-based study of 2,437 patients newly diagnosed with type 2 diabetes, obesity, diastolic hypertension, higher total cholesterol, and lower HDL cholesterol were independently associated with early onset type 2 diabetes. Both onset groups were on average obese (BMI >30 kg/m^2) (18,19), but those with early onset had a mean BMI 6 kg/m^2 greater than the usual-onset group at diagnosis (39 vs. 33 kg/m^2, respectively).

It is known that obesity increases the risk of developing type 2 diabetes (20,21). However, to our knowledge, no study has assessed obesity and age at onset in a population newly diagnosed with diabetes. We found a striking inverse linear relation between BMI and age at diagnosis of type 2 diabetes among adults who were on average obese in all but one age group (Fig. 1). The only exception was for adults diagnosed at age >70 years who were on average overweight (18) but not obese (Fig. 1). These results suggest that it is not a threshold of obesity that determines the risk of type 2 diabetes onset but rather a continuous relation of

risk within the obese range. Thus, it may be the degree of obesity that determines when diabetes will develop.

Obesity was the most striking difference between the onset groups, but hypertension and cholesterol were also notable. Although the absolute mean differences were not large for the hypertension and cholesterol variables between the two onset groups, it is remarkable that among the early onset group, 82% had abnormal lipids and half (49%) had hypertension at diagnosis. These results suggest that the insulin resistance syndrome is present at diabetes diagnosis in most young adults; presumably, these young adults will also have two to three times the risk of cardiovascular disease associated with this syndrome in older adults (21,22). The high prevalence of cardiovascular risk factors we observed at diagnosis in young adults is particularly alarming, as over half of the mortality in people with type 2 diabetes is from cardiovascular disease (23), and the incidence of macrovascular complications increases with duration (22,24).

Clinically, the higher prevalence of diastolic hypertension observed in younger adults with type 2 diabetes is quite concerning, even in the setting of lower systolic blood pressure and thus lower pulse pressure. Unlike adults >50 years of age, pulse pressure is not superior to systolic or diastolic pressure in predicting risk of coronary heart disease (CHD) in young adults (assessed in the Framingham cohort) (25). Because the risk for CHD in people with diabetes doubles when hypertension is also present (26), it is concerning that 49% of the early onset group already had either a systolic blood pressure >130 mmHg or a diastolic blood pressure >85 mmHg at the time of diabetes diagnosis.

In people with diabetes, HDL may be the best lipoprotein predictor of CHD (27). The mean HDL cholesterol was 33 mg/dl for adults with early onset type 2 diabetes, a value that would be categorized as high risk for CHD (27). Furthermore, for every 5-mg/dl decrease in HDL, the odds of early onset type 2 diabetes increased by 20%. The relative insulin deficiency that occurs in type 2 diabetes impairs the action of lipoprotein lipase and results in lower HDL levels and higher triglyceride levels, which may improve with improved glycemic control (28). However, worse glycemic control does
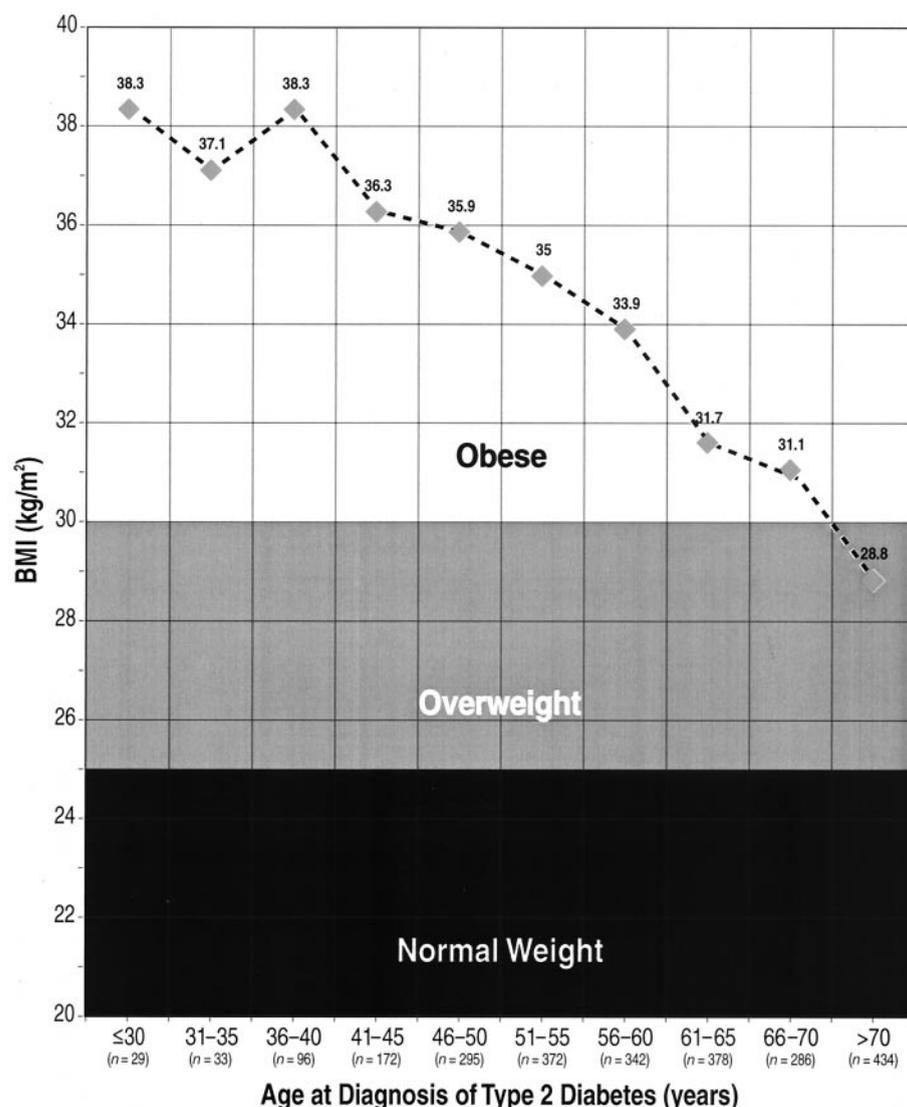
Figure 1—*Relation of BMI and age at diagnosis among people with newly diagnosed type 2 diabetes. P for trend <0.0001, based on linear regression of BMI on age at diagnosis.*

not explain the lower HDL we observed with early type 2 diabetes; lower HDL remained independently associated with onset group when HbA_{1c} was included in the multivariate model.

Both the younger and the older onset groups in our study had HbA_{1c} values <8% at diagnosis. KPNW has an aggressive diabetes treatment program, and the average HbA_{1c} of all members with prevalent and incident diabetes is 8.1%. With heightened diabetes awareness, it is possible for all adults to be diagnosed at an earlier stage than in other populations or practice settings. Therefore, the differences we observe in our study may underestimate the differences by onset group in other populations.

Any definition of type 2 diabetes is arbitrary because there are some patients that are difficult to classify as type 1 or type 2 diabetes, and this is particularly true with younger patients. Although we conservatively classified type 2 diabetes as no insulin use in the first year, this definition might preferentially exclude younger type 2 diabetic adults that are initially diagnosed as type 1 and then switched from insulin to oral agents in the first year after diagnosis. To rule out a potential misclassification bias, we identified all KPNW incident cases meeting study criteria who received insulin within the first 3 months of diagnosis but had no subsequent insulin dispenses months 4–12 in the first year after diagnosis (n =

62) and found that including these individuals enhanced rather than muted our metabolic findings, including BMI (data not shown).

Our results were found in a population diagnosed with type 2 diabetes, and we do not know whether the proportion of undiagnosed diabetes varies with age or whether undiagnosed young adults have better metabolic profiles. The ratio of undiagnosed to diagnosed diabetes was fairly constant among all age groups in the most recent National Health and Nutrition Examination Survey (1). Young adults represent the fastest growing age group for both obesity and type 2 diabetes over the last decade (6,5), and it is therefore likely that there may now be a higher proportion of undiagnosed young adults. However, as the prevalence of diagnosed diabetes at KPNW in 1997 (midstudy period) was 6.1% (unpublished data), closely matching the national temporal estimates (1,6), the proportion of undiagnosed diabetes in our population is likely similar to that of other populations. Finally, although the KPNW population is representative of the Portland metropolitan area ethnically and socioeconomically, our results may not be generalizable to other populations with different demographics.

Screening recommendations for type 2 diabetes in children and adults are changing (29), but a gap still exists for young adults <45 years of age. More importantly, many people in the medical and lay community do not routinely think of obese young adults as a high-risk group to screen for type 2 diabetes, despite recent evidence that adults 30–39 years of age are the fastest growing diabetic adult age group (5). The aim of the current study was to assess how metabolic profiles differ by age at diagnosis in adults and not to determine which young adults should be screened for type 2 diabetes. However, we hope the linear relation we observed between obesity and age of onset as well as the high prevalence of cardiovascular risk factors at diagnosis in young adults with type 2 diabetes will be used to strengthen screening strategies in very obese young adults, using the same principles that resulted in recent recommendations for obese children (29,30). More research is needed to determine the prevalence and characteristics of both diagnosed and undiagnosed young adults with type 2 diabetes so that we may better define which young adults would most benefit from screening and early intervention.

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