Complications of Dysglycemia and Medical Costs Associated With Nondiabetic Hyperglycemia

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Objective: To estimate the prevalence of complications associated with diabetes in patients with hyperglycemia below the threshold for diabetes, and to evaluate the associated medical costs.

Study Design: Retrospective observational cohort study.

Methods: We used fasting and random glucose test results, and a previously validated predictive equation to assign 26,111 nondiabetic patients to the following categories: normoglycemia, isolated impaired fasting glucose (I-IFG), isolated impaired glucose tolerance (I-IGT), or IFG with IGT (IFG/IGT). We identified microvascular complications (retinopathy, neuropathy, nephropathy) and macrovascular complications (cardiovascular disease, stroke, peripheral vascular disease, heart failure) commonly associated with diabetes from electronic medical records. We then calculated and compared the impacts of hyperglycemia and its complications in terms of age/sex–adjusted mean annual medical care costs.

Results: Complications were most prevalent among the I-IGT and IFG/IGT patients—more than half (51.1% in each group) had at least 1 complication compared with 33.9% of normoglycemic patients (P <.001 for both comparisons). Macrovascular complications added \$3863 (P <.0001) to annual age/sex–adjusted per-person medical costs; microvascular complications added \$1874 (P <.0001). I-IGT (\$716; P <.0001) and IFG/IGT (\$438; P = .009) independently added to costs after controlling for presence of any complication.

Conclusions: For many patients, complications associated with hyperglycemia appear to develop before diabetes diagnosis. Complications add significantly to the cost of medical care at hyperglycemic levels below the threshold for diabetes. However, the increased prevalence of complications did not completely explain the observed differences in age/sex–adjusted medical care costs.

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For author information and disclosures, see end of text.

Microvascular and macrovascular complications including retinopathy, neuropathy, nephropathy, and cardiovascular disease afflict the majority of patients with diabetes. The American Association of Clinical Endocrinologists recently reported that 58% of patients with diabetes have at least 1 complication, and about 25% have 2 or more.[1] That report also estimated that complications added about \$20 billion to the cost of diabetes treatment in the United States in 2006. The American Diabetes Association estimated that direct medical expenditures for diabetes in 2007 totaled \$116 billion, of which \$58 billion was attributed to the chronic complications of diabetes.[2]

Many of these costs may be avoidable through the prevention of diabetes and more intensive diabetes management. However, microvascular and macrovascular complications of hyperglycemia often predate the diabetes diagnosis. Greater prevalence of retinopathy and nephropathy has been associated with increasing hyperglycemia below the threshold for diabetes diagnosis.[3] In addition, data from the Framingham Heart Study offspring cohort showed an increased risk of chronic kidney disease among patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).[4] Two meta-analyses demonstrated that nondiabetic hyperglycemia is a risk factor for cardiovascular disease.[5,6]

These studies all indicate that nondiabetic hyperglycemia is a risk factor for microvascular and macrovascular complications. To our knowledge, however, no study to date has simultaneously estimated the prevalence of these complications in a general population of patients with hyperglycemia below the diagnostic threshold for diabetes. Furthermore, the medical costs of hyperglycemic complications before diabetes onset have not been described previously. We recently reported that medical costs were higher among patients with dysglycemia than among those with normoglycemia.[7] The objectives of the current study were to assess the prevalence of hyperglycemic complications among patients with IFG, IGT, or both relative to patients with normal glucose tolerance, and to determine the extent to which cost differences between patients with and without dysglycemia are explained by differences in microvascular and macrovascular complications.

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METHODS

Kaiser Permanente Northwest (KPNW) is a group model HMO that provides comprehensive healthcare to approximately 480,000 members, or about 20% of the population in the Portland, Oregon metropolitan area. As an integrated delivery system, KPNW provides all medically necessary healthcare to its members. The organization maintains electronic databases containing information on all inpatient admissions, outpatient visits, pharmacy dispenses, and laboratory tests. These databases are linked through the unique health record number members receive when they first enroll in the health plan. The institutional review board for the Kaiser Permanente Center for Health Research reviewed and approved this study.

To assess glycemic status, we applied the predictive equation developed and validated by Tabaei and colleagues (see **eAppendix**, available at **www.ajmc.com**).[8] We identified 33,895 nondiabetic patients (no mention of diabetes in the medical record and no antihyperglycemic medication) age 45 years or older who, between 1998 and 2004, had both a random (any value) and a fasting (<126 mg/dL) glucose test no more than 365 days apart. When multiple pairs of tests were available for an individual, we selected the most recent pair, assigning the latter of the 2 test dates as the patient's index date. Patients who developed diabetes during the year after the index date were excluded. Pregnant women and patients with malignant neoplasms, AIDS/HIV, or chronic renal failure also were excluded (n = 4584). In addition to random and fasting glucose values, the equation included coefficients for age, sex, body mass index, systolic blood pressure, and high-density lipoprotein cholesterol. We excluded 3200 patients who were missing data for 1 or more of these variables, for a final study sample of 26,111.

From results of the Tabaei et al logistic regression equation,[8] we used the recommended probability level (0.38) that provided optimal specificity (90%) to identify patients with and without dysglycemia, defined as IFG, IGT, or undiagnosed diabetes. In addition to the aforementioned variables, the Tabaei equation includes a coefficient for postprandial time. Because postprandial time was not available in our data, we assigned all patients a constant value of 3 hours, the mean reported by Tabaei et al. We then combined results from the equation with fasting glucose test results to assign patients to 1 of 4 categories. Patients who did not screen as dysglycemic with the algorithm were assumed to be normoglycemic if their fasting glucose level was <100 mg/dL, and were identified with isolated IFG (I-IFG) if their fasting glucose level was 100 to 125 mg/dL. Patients who screened as dysglycemic but had a fasting glucose level of <100 mg/dL were assumed to have isolated IGT (I-IGT). Those with a fasting glucose level of >100 mg/dL and a positive screen were defined as having IFG with IGT (IFG/IGT).

Since 1997, KPNW has used an electronic medical record system that captures up to 20 *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) physician-coded diagnoses at each patient contact. An electronic problem list also is part of the electronic medical record. We estimated (period) prevalence of the following hyperglycemic complications from the problem list and visit diagnoses that occurred 1 year before or after a patient's index date. Microvascular complications included retinopathy (*ICD-9-CM* codes 362.01, 362.02, 379.23); macular edema (*ICD-9-CM* code 362.83); and peripheral neuropathy (*ICD-9-CM* codes 354.2, 354.3, 355.2, 355.3, 355.6, 355.79, 355.9, 356.9, 357.1, 357.2, 357.4, 357.9). In addition, we used serum creatinine values to calculate estimated glomerular filtration rate using the Modification of Diet in Renal Disease Study formula.[9] We considered a value of <60 mL/min to be evidence of renal disease, and included this as a microvascular complication. Macrovascular complications included cardiovascular disease (*ICD-9-CM* codes 410.xx-414.xx); stroke (*ICD-9-CM* codes 430.xx, 431.xx, 432.xx, 434.xx, 435.xx, 436.xx, 437.1); peripheral vascular disease (*ICD-9-CM* codes 440.xx, 443.81, 443.9, 444.2x-444.8x, 445.0x); and congestive heart failure (*ICD-9-CM* code 428.xx).

For our cost analyses, we collected all medical utilization data for the 1-year period after each patient's index date (the latter of the random or fasting glucose test dates). Patients were required to be enrolled in the health plan for the entire 12-month period after the index date. Our costing method was based on procedures developed and validated by the Kaiser Permanente Center for Health Research that create standard costs for units of medical care (defined in the inpatient setting as direct hospital service components and in the outpatient setting as office visits).[10] Costs are identified from aggregate departmental expenditures rather than from procedure-specific charges or prices. Administrative costs and other indirect and joint costs are allocated to units of direct service using a variety of algorithms, developed either by the Center for Health Research (in the case of KPNW-produced inpatient services) or by the organization (in the case of outpatient visit and ancillary costs). This method has been described in detail elsewhere.[11] We multiplied standard unit costs by utilization volume to obtain total costs, inflated to 2005 US dollars. Before multivariate analysis, we log-transformed costs to account for the nonnormal distribution (adding $1 to those with zero costs), and adjusted them for age and sex using ordinary least squares (OLS) regression from a generalized linear model (SAS Proc GLM, SAS Institute, Inc, Cary, NC). Log transformation normalized the cost distributions. Prior research has demonstrated that simple OLS regression predicts costs as well as or better than more sophisticated modeling techniques.[11] For ease of interpretation, we report actual (nontransformed) costs estimates, displaying *P* values for both transformed and nontransformed models.

Table 1. Prevalence of Macrovascular and Microvascular Complications by Glycemic Status Category[a]

Characteristic	Normoglycemia	Isolated IFG	Isolated IGT	IFG/IGT
Patients, No. (%)	15,629 (59.8)	5713 (21.9)	2552 (9.8)	2217 (8.5)
Mean age[b] (SD), y	61.2 (10.7)	62.4 (10.4)	67.3 (11.7)	66.2 (11.1)
Percent female[b]	60.1	41.4	83.2	74.3
Macrovascular complications				
Cardiovascular disease				
Actual[c]	16.2	24.2	24.1	24.0
Age/sex adjusted[c]	17.5	21.5	23.2	22.8
Stroke				
Actual[d]	6.7	8.0	12.1	10.3
Age/sex adjusted[e]	7.6	8.1	10.1	8.8
Peripheral vascular disease				
Actual[c]	3.7	5.3	6.0	5.6
Age/sex adjusted	4.1	5.0	4.9	4.8
Congestive heart failure				
Actual[d]	4.6	7.0	10.4	12.0
Age/sex adjusted[d]	5.2	6.7	8.6	10.5
Any macrovascular complication				
Actual[d]	23.9	33.1	37.1	37.2
Age/sex adjusted[d]	25.8	30.6	33.9	34.1
Microvascular complications				
Retinopathy				
Actual	0.2	0.2	0.5	0.4
Age/sex adjusted	0.2	0.2	0.4	0.3
Macular edema				
Actual	0.3	0.3	0.4	0.5
Age/sex adjusted	0.3	0.3	0.3	0.5
Peripheral neuropathy				
Actual	6.5	6.8	8.0	8.2
Age/sex adjusted	6.7	6.9	7.0	7.5
GFR < 60 mL/min				
Actual[d]	11.0	12.9	23.1	21.0
Age/sex adjusted[d]	12.3	13.7	17.5	16.8
Any microvascular complication				
Actual[d]	14.8	17.2	27.7	25.9
Age/sex adjusted[d]	18.2	19.8	23.0	23.2
Microvascular and macrovascular complication(s)				
Actual[d]	6.3	8.7	14.5	12.9
Age/sex adjusted[c]	7.9	9.5	11.5	11.0
Any complication				
Actual[d]	31.6	41.0	49.7	49.1
Age/sex adjusted[d]	36.1	40.9	45.4	46.3

GFR indicates glomerular filtration rate; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
[a]Values are percentages unless otherwise indicated.
[b]All groups were significantly different (P <.001).
[c]Normoglycemia was significantly different from the other 3 groups (P <.001).
[d]All groups were significantly different (P <.001), except isolated IGT versus IFG/IGT (NS).
[e]Normoglycemia was significantly different from isolated IGT (P <.001).

■ Table 2. Descriptive Statistics for Total Medical Care Costs by Glycemic Status Category

Value	Normoglycemia	Isolated IFG	Isolated IGT	IFG/IGT
Mean	$6097	$6179	$7643	$7311
Standard deviation	$10,305	$9626	$10,741	$10,868
Median	$2859	$2981	$3855	$3554
Interquartile range	$1459-$6056	$1505-$6297	$1970-$8149	$1892-$7155
No. of patients (%) with zero costs	40 (0.15)	25 (0.10)	4 (0.02)	5 (0.02)

IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance.

We used the LSMEANS (least squares means) statement to compare mean annual age/sex–adjusted medical care costs across the 4 glycemic status categories, and to estimate age/sex–adjusted proportions with the various complications. In addition, we constructed 3 multivariate models to estimate the relative costs of hyperglycemic complications. The first model included each complication as an independent predictor of cost. In the second model, we collapsed the complications into 2 variables representing microvascular and macrovascular complications. The third model collapsed all complications into a single variable.

RESULTS

Of the 26,111 patients, 59.8% (n = 15,629) were defined as normoglycemic; they did not screen as dysglycemic using the Tabaei et al equation[8] and had a fasting glucose test result of <100 mg/dL (Table 1). Another 21.9% (n = 5713) did not screen as dysglycemic, but had a fasting glucose test result in the 100 to 125 mg/dL range and were therefore classified as I-IFG. Of those who did screen as dysglycemic, about half (n = 2552; 9.8% of total) had a fasting glucose result of <100 mg/dL and were classified as having I-IGT. The remainder (n = 2217; 8.5% of total) had a fasting glucose result of 100 to 125 mg/dL and were categorized as having IFG/IGT.

Age and sex were different across the 4 groups (*P* <.001 for all comparisons). With the exception of retinopathy and macular edema, statistically significant differences in all microvascular and macrovascular hyperglycemic complications were found among the groups. In general, complications were most prevalent among the I-IGT and IFG/IGT patients—more than half (51.1% in each group) had at least 1 complication. In contrast, 33.9% of patients with normoglycemia had at least 1 complication (*P* <.001 for both comparisons). For I-IGT and IFG/IGT patients versus patients with normoglycemia, prevalence of macrovascular complications (37.1% and 37.2% vs 23.9%; *P* <.001) and microvascular complications (27.7% and 25.9% vs 14.8%; *P* <.001) followed a similar pattern. Although adjustment for age and sex reduced the differences in prevalence of all complications between glycemic categories, statistical significance did not change (with the exception of peripheral vascular disease, which became nonsignificant).

Descriptive statistics for unadjusted total annual medical costs are provided in Table 2. The high standard deviation and large difference between mean and median costs indicates substantial variability and the nonnormal distribution commonly seen in medical cost data. However, very few patients had no costs in any of the glycemia groups.

Age/sex–adjusted annual medical costs for each of the individual complications are displayed in Table 3 (model 1). Peripheral vascular disease ($3824; *P* <.001 for logged costs), congestive heart failure ($4401; *P* <.001), and retinopathy ($4433; *P* = .021) were the most expensive complications, but all complications added significantly to the medical cost burden. After controlling for the individual complications, patients with I-IGT ($584; *P* <.001) or IFG/IGT ($297; *P* = .018) had additional medical costs relative to patients with normoglycemia. Model 2 shows that any macrovascular complication added $3863 (*P* <.001) to medical costs, whereas any microvascular complication added $1874 (*P* <.001). I-IGT ($639; *P* <.001) and IFG/IGT ($380; *P* = .015) independently added to costs after controlling for any microvascular or macrovascular complication. Model 3 indicates that the presence of any complication increased costs by $3496 (*P* <.001). Again, I-IGT ($716; *P* <.001) and IFG/IGT ($438; *P* = .009) significantly increased costs after controlling for any complication.

Figure 1 displays the annual age/sex–adjusted medical costs across the 4 glycemic status groups, stratified by presence or absence of hyperglycemic complications. Among patients with no complications, there were no statistically significant differences in medical costs according to glycemic status. However, among patients with any complication, those with I-IGT or IFG/IGT incurred significantly greater costs than those with normoglycemia or I-IFG ($9617 and $9314 vs $8525 and $8155; *P* <.001 for both comparisons).

Among patients with macrovascular complications, there were no statistically significant differences in total medical costs according to glycemic status (Figure 2). However,

Table 3. Multivariate Models of Total Medical Care Costs

Characteristic	Model 1[a] Parameter Estimate	Model 1[a] P	Model 1[a] Logged Cost P Value	Model 2[b] Parameter Estimate	Model 2[b] P	Model 2[b] Logged Cost P Value	Model 3[c] Parameter Estimate	Model 3[c] P	Model 3[c] Logged Cost P Value
Intercept (normal glucose)	$4544	<.001	<.001	$3900	<.001	<.001	$3091	<.001	<.001
I-IFG	($271)	.083	.521	($252)	.110	.498	($205)	.196	.707
I-IGT	$584	.008	<.001	$639	.004	<.001	$716	.001	<.001
IFG/IGT	$297	.196	.018	$380	.100	.015	$438	.059	.009
Age	$1	.887	<.001	$12	.068	<.001	$27	<.001	<.001
Female sex	$481	<.001	<.001	$411	.002	<.001	$271	.040	<.001
Cardiovascular disease	$2771	<.001	<.001	—		—	—		—
Stroke	$2230	<.001	<.001	—		—	—		—
Peripheral vascular disease	$3824	<.001	<.001	—		—	—		—
Congestive heart failure	$4401	<.001	<.001	—		—	—		—
Any macrovascular complication	—	—	—	$3863	<.001	<.001	—		—
Retinopathy	$4433	<.001	.021	—		—	—		—
Macular edema	$2081	.064	.007	—		—	—		—
Peripheral neuropathy	$2233	<.001	<.001	—		—	—		—
GFR <60 mL/min	$946	<.001	<.001	—		—	—		—
Any microvascular complication	—		—	$1874	<.001	<.001	—		—
Any complication	—		—	—		—	$3496	<.001	<.001

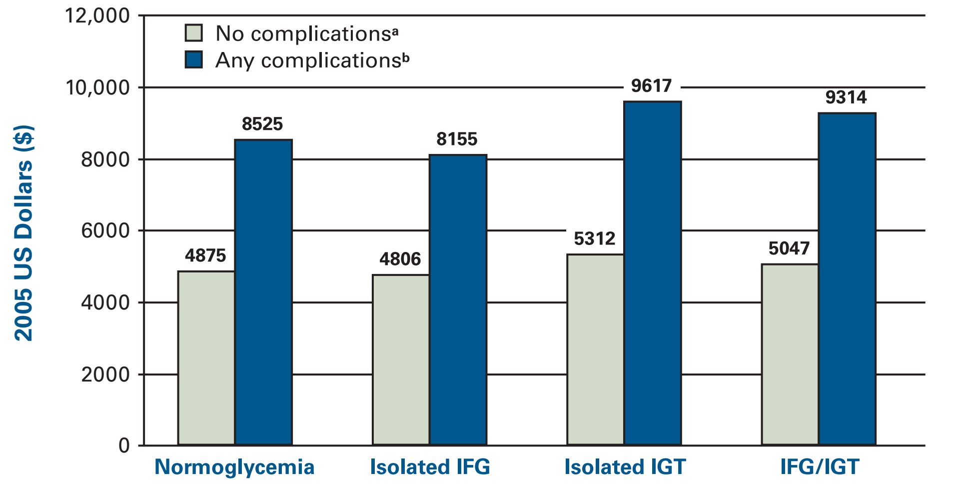
GFR indicates glomerular filtration rate; IFG/IGT, impaired fasting glucose with impaired glucose tolerance; I-IFG, isolated impaired fasting glucose; I-IGT, isolated impaired glucose tolerance.
[a]Model 1 includes separate variables for each specific complication.
[b]Model 2 collapses specific microvascular and macrovascular complications into 2 variables.
[c]Model 3 collapses microvascular and macrovascular complications into a single variable.

inpatient costs for those with macrovascular complications differed significantly between I-IGT patients and those with I-IFG or normoglycemia. Among patients with microvascular complications (Figure 3), those with IFG/IGT ($9710) incurred significantly greater total costs than those with normoglycemia ($8657; P = .001) or I-IFG ($8046; P <.001). The I-IGT patients also incurred higher total costs than the normoglycemic or I-IFG patients (P = .008 and .003, respectively). Inpatient costs were largely responsible for the significant differences.

DISCUSSION

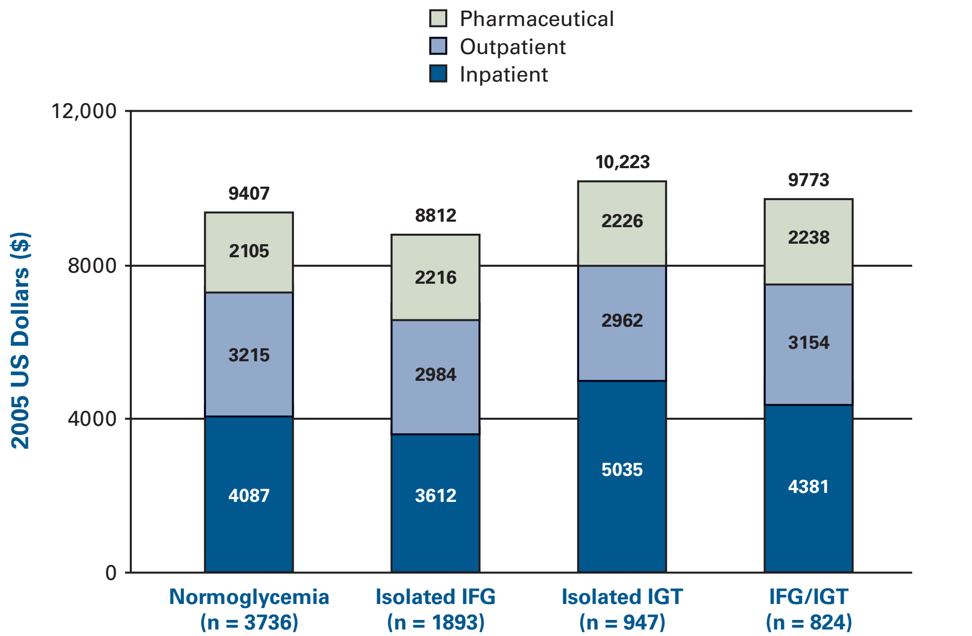
In this observational cohort study of more than 26,000 individuals, we found that patients with IGT (either isolated or in combination with IFG) had significantly more microvascular and macrovascular complications than patients with normoglycemia. The prevalence of complications also was increased among patients with I-IFG relative to patients with normoglycemia, though not to the same degree. The observed differences between glycemic status groups were most distinct for microvascular complications, particularly for renal disease. However, macrovascular disease was more prevalent than microvascular disease in all glycemic status groups. We found that 43% to 51% of patients with nondiabetic dysglycemia had at least 1 complication, a prevalence rate only slightly lower than the 58% recently estimated among patients with diabetes.[1] Thus, for many patients, microvascular and macrovascular complications commonly associated with diabetes appear to develop before diabetes diagnosis.

Figure 1. Annual Age/Sex–Adjusted Medical Care Costs by Glycemic Status and Presence of Complications



IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance.
[a]No glycemic status group comparisons were significantly different (P <.001).
[b]All comparisons were significantly different (P <.001), except normoglycemia versus isolated IFG and isolated IGT versus IFG/IGT.

Figure 2. Annual Age/Sex–Adjusted Medical Care Costs Among Patients With Macrovascular Complications, by Glycemic Status[a]

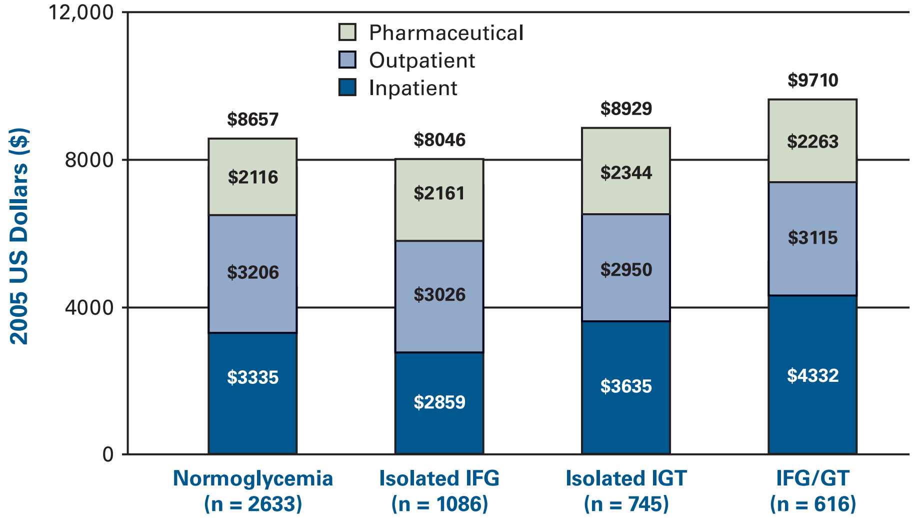


IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance.
[a]No comparisons of (logged) total costs were significantly different at P <.001. However, inpatient costs differed significantly between the isolated IGT group and the isolated IFG and normoglycemic groups (P <.001).

The increased prevalence of complications among patients with dysglycemia did not completely explain the observed differences in age/sex–adjusted medical care costs. Although costs for patients with I-IFG were similar to those for normoglycemic patients, I-IGT and IFG/IGT independently accounted for additional costs after controlling for the presence of complications. This effect appeared to be concentrated in patients with microvascular complications; a subanalysis of patients with no complications and another of patients with macrovascular complications yielded no significant differences in comparisons of the 4 glycemic status groups. It is also important to note that other comorbidities did not explain costs differences. With the exception of cataracts (8.9%) and arthritis (5.0%), no specific condition accounted for more than 3% of hospitalizations, and the incidence of those 2 conditions was equal across groups.

Despite excluding patients with chronic renal failure, renal dysfunction accounted for the majority of microvascular complications in our data. Thus, the elevated costs we observed may be largely attributable to chronic kidney disease, a finding consistent with a previous report in this setting.[12] There is strong evidence that intensive glycemic control can delay the onset of microalbuminuria and prevent progression from microalbuminuria to macroalbuminuria in patients with diabetes.[13-15] Given the enormous cost of renal failure, early attention to hyperglycemia appears warranted.

■ **Figure 3.** Annual Age/Sex–Adjusted Medical Care Costs Among Patients With Microvascular Complications, by Glycemic Status[a]



IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance.
[a]Total (logged) costs for the IFG/IGT group differed significantly from those for the normoglycemic (P = .001) and isolated IFG (P <.001) groups. Total costs for the isolated IGT group differed significantly from those for the normoglycemic (P = .008) and isolated IFG (P = .003) groups. Inpatient costs were significantly different between all groups (P <.001), except normoglycemia versus isolated IFG and isolated IGT versus IFG/IGT.

In developing the predictive equation we used, Tabaei et al reported specificity of 90%, sensitivity of 55%, and positive predictive value of 65%.[8] Even if the equation performed as well as or better in our population, we undoubtedly misclassified some individuals. Because we did not have oral glucose tolerance test results available, we could not assess the accuracy of the equation in our own data. Nevertheless, the clinical and demographic characteristics of the groups we created were consistent with the known characteristics of patients with IFG and IGT.[16] Furthermore, misclassification is most likely to occur among normoglycemic patients who should in fact be classified as having IGT. If so, the complication prevalences and costs we reported for the patients with normal glycemia would be artificially elevated. Thus, our results may well be conservative.

An important limitation of the current study is that we required patients to have both a random and a fasting glucose test no more than 1 year apart. Because the tests typically did not occur on the same day (the mean number of days between tests was 210), it is possible that glucose homeostasis changed from one test to the other, which could result in misclassification. Furthermore, by requiring 2 tests that rarely occurred simultaneously, we may have identified patients who were seeking an explanation for ill health, and were therefore at greater risk of adverse health events. That may have inflated our prevalence estimates of hyperglycemic complications. Indeed, 34% of our dysglycemic study sample had at least 1 macrovascular complication, which is slightly higher than the 31% of patients with diabetes found to have cardiovascular disease in the same setting.[17] On the other hand, previous reports indicate higher prevalences of peripheral vascular disease[18,19] and retinopathy[20,21] than those we found, whereas our estimate of the prevalence of peripheral neuropathy was similar to that in 1 prior study.[19] Because so few population-based hyperglycemia studies are available, and none assessed all hyperglycemic complications simultaneously, it is difficult to determine the precision of our estimates.

Consistent with prior studies, we found that microvascular and macrovascular complications were more prevalent in patients with glycemic levels below the threshold for diabetes relative to normoglycemic patients. Complication rates were particularly high when IGT was present, a hyperglycemic state not typically assessed in the United States. It is not yet known whether early detection and treatment of patients at risk of developing diabetes can prevent additional complications from developing. However, if emerging research suggests complications can be avoided with diabetes prevention, earlier detection and treatment may provide substantial economic benefit to society and improved health for individual patients.

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Authorship Information: Concept and design (GAN, BA, WHH); acquisition of data (GAN); analysis and interpretation of data (GAN); drafting of

Take-away Points

Nondiabetic patients with impaired fasting glucose and/or impaired glucose tolerance often have complications normally associated with diabetes, but these complications do not fully explain why their costs are higher than patients with normal glycemic levels.

- Nearly half of dysglycemic patients had at least 1 complication, compared with less than one third of normoglycemic patients.
- Macrovascular complications added $3863 to annual per-person medical costs, while microvascular complications added $1874.
- Impaired glucose tolerance, but not impaired fasting glucose, independently accounted for additional costs after controlling for the complications, an effect that was concentrated in patients with microvascular disease.

the manuscript (GAN); critical revision of the manuscript for important intellectual content (BA, WHH); statistical analysis (GAN); obtaining funding (GAN, BA); and administrative, technical, or logistic support (WHH).

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