

Joslin Diabetes Fifty-Year Medalist Study Update

May 2007

In the three years since the start of the second phase of the Joslin 50-Year Medalist study, we have studied over 275 Medalists who have traveled to Joslin. In addition, we are scheduled to study another 150 Medalists in the last year of this study. To those who have already participated, we would like to thank you for all your efforts and help. For those of you who are scheduled to come during the next few months, we are looking forward to meeting you and learning from you. In the following, I will provide a brief summary of the results that we have obtained thus far.

In the first phase of the study, which took place three years ago, we asked many of you to fill out an extensive questionnaire and provide some laboratory data from your doctor. The results from these questionnaires and lab results provided the very interesting finding that close to 50% of you appear to have escaped complications which occur in almost all diabetic patients by 30 years of duration. These complications include eye disease (retinopathy), kidney disease (nephropathy) and nerve disease (neuropathy). Further, we have found that both genetic and metabolic factors are important in the prevention of complications in type 1 diabetic patients. The results showed that as a group, Medalists have controlled their glucose very well for many years. In addition, hemoglobin A1c, a measure of chronic glucose control, does not seem to

correlate with the various complications described above. This means that the long survival of Medalists is due to both their own efforts in controlling diabetes and their genes, which protect them from the adverse effects of elevated glucose levels. These are very exciting findings which will be published in the journal *Diabetes Care* in the next few months.

In the second phase of the study, we are bringing many of you to Joslin and examining the status of your complications with respect to your eye, kidney, nerve and heart function. We are also studying the metabolic changes in your blood and your body's ability to produce insulin. We are also studying your genes in order to determine whether you have typical type 1 diabetes or a different, yet unknown type, and whether your body is still producing auto-antibodies against insulin producing cells found in the pancreas. Data from over 200 of you have been analyzed and we have made very exciting discoveries. The data showed that most of you have clinical and laboratory findings consistent with patients who have been identified with "typical" type 1 diabetes. We have confirmed the results of the questionnaire to show that the parameters of glucose control such as hemoglobin A1c and glycated albumin do not correlate with the presence of eye, kidney and nerve dysfunction in the Medalists. The eye studies, which took pictures of the back of the eye, showed that about 40% of the Medalists do not have significant eye disease even after 50-80 years of type 1 diabetes. In addition, we also analyzed the lipid or fat profile of blood samples, which showed that many of you have elevated levels of HDL, the good cholesterol that protects people from developing cardiovascular disease. From a complications point of view, these findings are very exciting since they showed that 40% of the Medalists have factors or genes, which have protected them from developing diabetic eye disease. In the next phase of this study, we are planning to perform genetic studies with the hope of detecting genes which can protect all diabetic patients from developing complications. The

results are clearly telling us that further genetic studies are needed in order to find these diabetes complication-preventing genes.

In addition to the exciting findings regarding diabetic complications, the results from the Medalists have also yielded an unexpected finding regarding your pancreatic functions. Surprisingly, the pancreas of over 20% of Medalists appear to produce a small amount of insulin. This finding is clearly very important and exciting since it suggests that in some type 1 diabetic patients the pancreas, which makes insulin, may still be functional after 50-70 years duration. If this finding can be confirmed, then it raises the possibility that many type 1 diabetics who have fewer years of diabetes may continue to have functional pancreatic tissues that could make insulin. Thus, in the last few months and in the near future, we have/will bring some of the Medalists back to Joslin for further studies to determine whether their pancreatic islets can potentially make insulin in response to various known stimulations of insulin secretion.

In the above, I have summarized the new findings from the Medalist study, which have clearly suggested that we should do the following.

- 1.) Further genetic studies are needed to determine which genes are present in approximately 40% of the Medalists that are protective factors for preventing blood vessel problems.
- 2.) New stimulation tests are needed in order to determine whether some of the Medalists still have functional insulin producing islets after such a long time with type 1 diabetes.
- 3.) Further collections from new Medalists must be done in order to continue the study and gather more data.

As I stated above, we are in the last year of funding from the Juvenile Diabetes Research Foundation. We have also received support from Eli Lilly and Company and generous donations from many Medalists over the last two years, which has allowed us to embark on this large and

groundbreaking study. I would like to specifically mention Mr. Bill and Dee Brehm (Medalist) and Mr. Tom Beatson (Medalist) for their continued support which allows us to perform many of these special and costly studies at such a rapid pace. Hopefully, we can continue and renew our support from the Juvenile Diabetes Research Foundation and obtain new support from other foundations which will allow us to achieve the three goals stated above. I also would like to mention that the Medalist team consists of Mrs. Alysha Berger, who many of you have met or contacted during your visits to Joslin, and Dr. Hillary Keenan, whose main interest is in the genetic factors which make this population so extraordinary. Recently, we have also been joined by Drs. Jennifer Sun and Lloyd Paul Aiello, both of whom are ophthalmologists working to document and analyze the findings in the eyes of Medalist patients. Lastly, I would again like to thank all of the Medalists for coming to Joslin and those who are scheduled to come in the near future. None of the studies would be possible without your immense contribution. I look forward to working with all of you in order to understand the wonderful secrets that you all hold, which could potentially lead to new treatments of diabetes and its complications.

Sincerely,



George King, MD

Clinical Factors Associated with Resistance to Microvascular Complications in Diabetic Patients of Extreme Disease Duration: The Fifty-Year Medalist Study

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Running title: Limited complications in extreme diabetes duration patients

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INTRODUCTION

Duration of diabetes and degree of hyperglycemia have been identified consistently as predictors of retinopathy (DR) and nephropathy (1-6). Multiple studies have concluded that nearly all individuals with type 1 diabetes (T1DM) will develop some level of retinopathy within 20 years of diagnosis (2,4,5,7,8). However, the study by Bain et al (9), who described in the Golden Years Study group of type 1 diabetic patients with 50 or more years of duration appeared to be protected against nephropathy and large vessel disease, but not against retinopathy. However, the associations of glycemic control, duration of disease and vascular complications were not evaluated (9). This report characterizes the prevalence of complications and associated risk factors in a large number of individuals who have been insulin dependent for 50 or more years.

METHODS

The Joslin Diabetes Center's (JDC) Fifty-Year Medal Program was initiated to recognize Joslin or non-Joslin patients who survived fifty or more years with T1DM. This was documented either by medical record or family report. This was a survey based cross-sectional study of Medalists living in the United States who were awarded the Joslin Medal between 1997 and 2003. The Committee on Human Subjects at the JDC approved this Study. The patients were questioned regarding the presence and absence of eye, kidney and peripheral neuropathy.

Clinical Validation of Retinopathy:

Self-reported retinopathy was validated by comparing retinal clinical examination and fundus photography (7-standard field) in a subset (N= 92, 28%) of the 326 medalists, to the questionnaire with the worse eye used for analysis. Grading was performed by two

experienced ophthalmologists and discrepancies adjudicated by consensus. Descriptive analyses were performed using the Statistical Analysis System v8.2 (Cary, NC). The Cochran-Armitage test was used to test for trends of categorical variables. Logistic regression was used to estimate the association of microvascular complications with risk factors

RESULTS

A total of 405 (81%) out of 500 Medalists responded to the initial questionnaire; the remaining 95 (19%) were returned with incorrect addresses. Twenty-one individuals (62%) who returned the initial questionnaire did not wish to participate; seven (5.1%) were too ill; thirteen (33.3%) were not interested and one (4.7%) did not provide a reason. As of January 2004, 326 of 405 questionnaires had been completed (81%) with 21% receiving regular care from JDC.

Of the 326 respondents, 54.7% were female. The average age at the time of completing the questionnaire, and at diagnosis of T1DM were 69.5 ± 8.4 and 12.6 ± 7.1 years, respectively. The mean body mass index (BMI) was $24.5 \text{ kg/m}^2 \pm 4.0$. The median of most recent physician reported HbA1c was 7.0% (range: 4.7-10.8%) and the average insulin dose per kilogram was 0.5 ± 0.2 (u/kg).

Microvascular complications

A total of 174 (53.4%) individuals reported microvascular complications (Table 1). Triglycerides ($p=0.05$), insulin dose per kilogram ($p=0.02$), and insulin dose ($p<0.05$) were higher among Medalists who reported a complication (retinopathy, nephropathy, neuropathy), compared to those not reporting any microvascular problems (Table 1). Age, diabetes duration, age at onset of diabetes, HbA1c, BMI, total cholesterol, and LDLc did not differ significantly between groups or for

each microvascular complications. HDLc levels were higher in Medalists who did not report any microvascular complications (71.6 ± 30.9 mg/dL vs 64.5 ± 25.0 mg/dL, $p=0.06$).

Current regular physical activity was associated with a reduced risk of complications (OR: 0.3, 95% CI: 0.13, 0.54), as well as, individually associated with decreased risk of retinopathy (OR: 0.48, 95% CI: 0.26, 0.92), nephropathy (OR: 0.33, 95% CI: 0.13, 0.87), and neuropathy (OR: 0.27, 95% CI: 0.14, 0.53). Exercise was not protective among those with an HDLc level greater than the median (65 mg/dL, OR= 0.35, 95%, CI: 0.11, 1.08). However, regular exercise was associated with significantly lower risk among those with HDLc levels below the median (OR: 0.22, 95% CI: 0.07, 0.70). Prevalence of retinopathy, nephropathy and neuropathy did not differ across quartiles of HbA1c.

Retinopathy

One hundred and thirty-nine (47.9%) Medalists reported DR (see supplement for assessment). Those without DR were older ($p<0.01$), had longer diabetes duration ($p<0.01$) and lower triglyceride levels ($p=0.04$) than those with DR (Table 1). Among Medalists, retinopathy prevalence declined with increasing duration. Reported prevalence of DR was 50% (107/213), 44% (29/66) and 27% (3/11) for durations of 50-59, 60-69, and greater than 69 years, respectively.

Nephropathy

A small number of Medalists reported nephropathy ($n=22$, 6.7%). Affected individuals were younger at diagnosis ($p=0.05$), had heavier BMI (<0.01), lower HDLc levels ($p=0.01$), higher triglycerides ($p<0.01$), and more frequently reported heart problems ($p=0.05$) than those who did not report nephropathy.

Neuropathy

Over half of Medalists reported neuropathy ($n=164$). Compared to Medalists without neuropathy, these patients had a higher insulin dose per kilogram ($p=0.02$), lower HDLc levels ($p=0.04$), higher triglycerides ($p<0.01$), and more heart disease ($p<0.01$).

Validation

90% of the patients studied ($n=92$) for validation correctly reported their DR status. In these individuals, 42 (51.9%) had no, mild or moderate evidence of retinopathy, 39 (48.1%) had proliferative DR. Six individuals without DR self-reported the complication, and only five individuals with DR reported no DR. The mean historical corrected HbA1(c) values had a strong correlation with a patients' current HbA1c level ($p<0.01$, $R=0.7$).

DISCUSSION

The Medalists demonstrated several unexpected vascular findings. One feature is that close to half (46.8%) did not report any significant microvascular complications and only approximately 50% of those with 50 to 60 years duration reported DR, and this **decreased** to only 44% and 27% at 60-69 years and 70 or more years of diabetes, respectively. This is in contrast to the literature which reports that over 90% of type 1 diabetes patients will eventually develop retinopathy (2, 4, 7). Another unexpected finding is the lack of association between glycemic control and prevalence of reported microvascular complications in Medalists that was not addressed by Bain et al (9). Most studies involving diabetes have shown that the risk for microvascular complications is strongly associated with glycemic control (3-6,11,12). These data suggest that individuals with extreme duration of T1DM are either protected from or have markedly slower progression of DR. These novel findings might result from either a reduction in factors which promote the disease, such as

hyperglycemia, or an increase in factors inhibiting the disease. Another possible reason, a reporting bias towards the complication free group is unlikely since validation studies showed close approximation of fundus photography with reported retinopathy.

A mean HDLc level of 67.7 ± 27.6 mg/dL in the Medalists is high for T1DM patients, but, this is consistent with the Golden Years Study (9). In the Cardiovascular Health Study, healthy aging men with HDLc levels of 60.4 mg/dL or higher were found to be at a lower risk for many common causes of death (13, 14). HDLc levels are influenced by multiple factors including genetics and physical activity (14-16). In this study exercise was associated with reduced microvascular complications but not in those with HDLc above the median. These results suggest that exercise may be an important protective factor, especially when HDLc levels are not elevated. Genetic factors may also be important since the mean age of death was

73.6 (± 13.6) years for the father and 78.4 (± 14.2) years for the mother of the Medalist. The life expectancy for this birth cohort (ca.1900) was 47.6 years for Caucasians of both sexes (17).

The Medalist Study showed that significant numbers of diabetic patients could live without severe complications for an extreme duration of the disease, suggesting they may contain factors that can neutralize the adverse effects of hyperglycemia.

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Table 1. Characteristics of Medalists broken down by complication status. Mean \pm standard deviation (25-75 percentile range)

	Retinopathy		Nephropathy		Neuropathy		P
	N	P	N	P	N	P	
M/F	Yes	139	22	164	174		
	No	151	304	145	152		
Age (years)	Yes	62/77	7/15	80/84	83/91	0.30	0.6
	No	72/79	144/160	63/82	68/84		
Duration of Diabetes (years)	Yes	67.7 \pm 7.5	66.4 \pm 7.7	69.0 \pm 8.0	68.8 \pm 7.9	0.30	0.75
	No	71.3 \pm 8.9	69.8 \pm 8.4	70.1 \pm 8.7	69.1 \pm 8.0		
Age at onset (years)	Yes	56.1 \pm 5.6	57.5 \pm 5.7	56.9 \pm 5.9	57.0 \pm 5.9	0.87	0.70
	No	58.1 \pm 6.3	57.2 \pm 6.0	57.6 \pm 6.1	57.3 \pm 5.9		
BMI (kg/m ²)	Yes	11.9 \pm 7.1	9.8 \pm 6.1	12.7 \pm 6.9	12.4 \pm 6.7	0.05	0.64
	No	13.6 \pm 7.4	12.8 \pm 7.2	12.6 \pm 7.3	11.9 \pm 6.9		
Daily Insulin dose (u)	Yes	24.9 \pm 3.8	27.0 \pm 3.3	24.6 \pm 3.8	24.7 \pm 3.8	<0.0 ₁	0.56
	No	24.1 \pm 4.2	24.4 \pm 4.0	24.4 \pm 4.2	24.4 \pm 4.3		
Insulin dose (u/kg)	Yes	33.8 \pm 15.2	41.2 \pm 18.8	34.9 \pm 16.0	34.9 \pm 15.8	0.01	<0.01
	No	32.3 \pm 14.6	32.2 \pm 14.2	30.3 \pm 12.7	30.2 \pm 12.9		
HbA1c (%)	Yes	0.5 \pm 0.2	0.53 \pm 0.2	0.5 \pm 0.2	0.5 \pm 0.2	0.3	0.02
	No	0.4 \pm 0.2	0.4 \pm 0.2	0.4 \pm 0.2	0.4 \pm 0.2		
HDLc (mg/dL)	Yes	7.1 (5.5, 9.9)	7.4 (5.7, 9.5)	7.1 (5.2, 9.9)	7.0 (5.2, 9.9)	0.21*	0.38*
	No	7.0 (4.7, 10.8)	7.0 (4.7, 10.8)	7.0 (4.7, 10.8)	7.0 (4.7, 10.8)		
Triglyceride (mg/dL)	Yes	74.5 \pm 32.7	53.8 \pm 19.5	64.3 \pm 25.1	64.5 \pm 25.0	0.01	0.06
	No	66.2 \pm 70.4	68.5 \pm 28.0	71.7 \pm 30.4	71.6 \pm 30.8		
Hypertension (%)	Yes	90.3 \pm 57.8	142.6 \pm 79.3	91.6 \pm 58.0	90.9 \pm 57.6	<0.0 ₁	0.05
	No	76.4 \pm 43.6	79.1 \pm 46.5	72.3 \pm 39.0	72.6 \pm 39.4		
*Non-parametric test p value	Yes	52.5	61.9	56.9	56.8	0.30	0.2
	No	53.6	50.5	48.7	45.1		



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Embargoed Until Monday, June 12, at 8 a.m. Eastern Time

Joslin Scientists Discover Surprising Signs of Residual Islet Cell Functioning in People with Type 1 Diabetes in the 50-Year Medalist Study

*Study to be presented June 12 at the American Diabetes Association's
66th Scientific Sessions in Washington, D.C.*

BOSTON -- Scientists at Joslin Diabetes Center have discovered that a surprisingly high percentage of people with type 1 diabetes (insulin-dependent) who have had the disease for 50 years or longer (The Joslin Medalists) may still have residual functioning, insulin-producing islet cells and/or islet cell antibodies. The findings will be presented June 12 at the American Diabetes Association (ADA) 66th Annual Scientific Sessions in Washington, D.C.

“It is surprising that some Medalists still have c-peptide secretion, a sign of insulin production, and some are positive for antibodies to the islets, another sign that some islet function or mass still is present. The significance of these findings is that even after such a prolonged period of diabetes, some patients still have residual islet function,” said George L. King, M.D., the study's lead author. Dr. King is Joslin's Research Director, Head of the Section on Vascular Cell Biology, head of Joslin's 50-Year Medalist Study and a Professor of Medicine at Harvard Medical School.

In addition, the researchers found 48 percent of the total participants reported no or very little microvascular complications, such as kidney and eye problems, which demonstrates that long duration of diabetes does not always progress to complications. There also was no significant

difference in age, duration, age of onset or long-term glucose control measured by A1C (glycated hemoglobin) levels between those with or without complications.

This talk is one of nearly 80 presentations to be delivered by Joslin scientists at the ADA's Scientific Sessions, Friday, June 9, through Tuesday, June 13. Some 15,000 scientists, physicians and health professionals will attend the conference, to be held at the Washington Convention Center. **The talk, "Immune Tolerance and Other Treatment Approaches for Type 1 Diabetes," is scheduled for June 12 at an 8–10 a.m. EST session on Immunology/Transplantation. [Abstract Number 278-OR: "Positivity of C-peptide, GADA and IA2 antibodies in Type 1 Diabetic Patients with Extreme Duration"]**

Since 1970, Joslin Diabetes Center in Boston has awarded medals or certificates to people with type 1 diabetes who have been insulin-dependent continuously for at least 25 years. To date there have been approximately 2,400 50-Year Medals awarded and 17 distinctive 75-Year Medals. The Medalist Study began in April 2005 to identify physiological, clinical, genetic and other factors shared by the Medalists.

The study being presented at the ADA meeting is part of the second phase of the Joslin 50-Year Medalist Study that is assessing these factors in 326 patients with more than 50 years of insulin-dependent diabetes. It evaluated a subset of 125 people with type 1 diabetes for biomarkers of insulin function. Of this group, 12.7 percent had a c-peptide level greater than 0.3 ng/mL, which indicates active islet cells and some residual insulin production. Most of the Medalists have the characteristics associated with type 1 diabetes with or without the presence of c-peptide.

In addition, 23.2 percent of the c-peptide positive participants produced either of two antibodies, GADA and IA2, which attack islet cells. The study also found that 17 percent of participants who were not c-peptide positive produced GADA or IA2 antibodies to the islet cells, another indication that a small amount of islet cells may still be present and/or functioning.

"The findings are phenomenal," said Hillary Keenan, Ph.D., research associate at Joslin and co-investigator on the 50-Year Medalist Study, who will present the findings. "This is the first study to look at the specific biomarkers for islet cell presence in people with a 50-year duration of insulin-dependent diabetes." Other Joslin investigators in the study included Alessandro Doria, M.D., Ph.D., Lloyd Paul Aiello, M.D., Ph.D., Korey Hood, Ph.D., and Jennifer Sun, M.D.

The group also was tested for other clinical parameters, such as cholesterol, triglycerides, body mass index and daily insulin dose. The data shows no significant difference in clinical parameters for participants with or without c-peptide. For example, the average total cholesterol of the c-peptide positive participants was 146 compared to 162 for the participants who did not produce c-peptide.

“If we could find out the reason for their lack of complications, we could perhaps prevent kidney or eye disease,” said Dr. King. The study has been investigating whether other factors, such as lifestyle or longevity genes, play a role in the development of complications, reported Dr. Keenan.

Overall, the study opens new avenues for research and treatment of type 1 diabetes. “The findings suggest that many patients, even after many years of diabetes, may still have some residual islet function. If a way can be found to stimulate islet growth, we could improve their diabetes and reduce insulin usage or better control blood glucose levels. If islets were returned to normal levels, they wouldn't need to take insulin,” said Dr. King.

Of the 326 Joslin 50-Year Medalist Study respondents who have completed an extensive health questionnaire, 175 were female and 151 were male, with an average age of 70 years. The average age of diabetes onset was 13 years and average duration of type 1 diabetes 57 years. The data collected so far show that individuals who have survived 50 years or more have a greatly reduced risk of nephropathy and retinopathy.

Funding for the study was provided by the Juvenile Diabetes Research Foundation.

About Joslin Diabetes Center

Joslin Diabetes Center, dedicated to conquering diabetes in all of its forms, is the global leader in diabetes research, care and education. Founded in 1898, Joslin is an independent nonprofit institution affiliated with Harvard Medical School. Joslin research is a team of more than 300 people at the forefront of discovery aimed at preventing and curing diabetes. Joslin Clinic, affiliated with Beth Israel Deaconess Medical Center in Boston, the nationwide network of Joslin Affiliated Programs, and the hundreds of Joslin educational programs offered each year for clinicians, researchers and patients, enable Joslin to develop, implement and share innovations that immeasurably improve the lives of people with diabetes. As a nonprofit, Joslin benefits from the generosity of donors in advancing its mission. For more information on Joslin, call 1-800-JOSLIN-1 or visit www.joslin.org.