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DIABETES MELLITUS IN THE EXTREME LONGEVITY

M. Motta^{a*}, E. Bennati^a, M. Capri^b, L. Ferlito^a, M. Malaguarnera and IMUSCE^{**}

^aDepartment of Senescence Sciences, University of Catania, Cannizzaro Hospital, Via
Messina, 829, I-95126 Catania, Italy

^bDepartment of Experimental Pathology, University of Bologna,
Via S. Giacomo 12, I-40126 Bologna, Italy

*Corresponding author:

Phone: +(39-095)-726-2050;

Fax: +(39-095)-498-811

E-mail: lmotta@unict.it

**For IMUSCE see Appendix 1.

Abstract

Epidemiological studies have revealed a progressive increase in the prevalence of diabetes mellitus in the elderly. Numerous factors are responsible for this trend, among them there are a) the long lasting disease due the improved therapeutic remedial (pharmacological, dietary treatments and physical activity), (b) the increased life span expectancy. The prevalence of diabetes mellitus in long living subjects is lower than in elderly people (subjects aged from 65 to 84). Senile diabetes is prevalent in long living people, and usually begins after 90 years. The incidence of neodiagnosed diabetes is higher in the oldest old than in the elderly people. Based on the results, diabetes mellitus is a negative factor for survival, and does not usually allow to achieve very old age, i.e centenarian.

Keywords: longevity, senile diabetes, centenarians

1. Introduction

Epidemiological studies have revealed a progressive increase in the prevalence of diabetes mellitus in the elderly. Several factors are responsible for this trend, among them are (a) the long lasting disease due to improved therapeutic remedies (pharmacological, dietary treatments and physical activity) (Laaksonen et al., 2005; Miggiano et al., 2006; Uusitupa et al., 2000), (b) increase life span expectancy (Wilson et al. 1986; ILSA Group, 1997; Stolk et al., 1997).

It has been estimated that 7.3% of individuals which aged ranged from 20 to 79 years and belonging to IDF countries develop diabetes (IDF, 2007). It should be mentioned that different epidemiological studies display significative deviance of diabetes prevalence in the elderly (from 10 to 38 %) with respect to the year of the study, the ethnic groups and also on the applied diagnostic criteria (ILSA Group, 1997; Meneilly and Tessier, 2001).

In 1979 the established diagnostic criteria for diabetes was the measurement of fasting blood glucose with value ≥ 140 mg/dl (National Diabetes Data Group, 1979). Later on this criteria was confirmed by the World Health Organization (WHO, 1985, 1992). However, from 1997, the glycemic value was lowered to ≥ 126 mg/ that should be measured in the morning (ADA, 1997; Alberti and Zimmet, 1998).

Due to these changes, the epidemiological data published until 1997 showed lower prevalence of diabetes, than more recent studies in which are applied the new rigorous ADA (1997) and WHO (1998) criteria.

Lately, also the sanitary system has recognized prevention as the best cure and this is resulting in more frequent blood analysis. As a consequence, there is an increased knowledge in the diabetes pathology, and it has been seen that senile diabetes appearing after 65 years of age, shows only a few symptoms. In addition, oral glucose tolerance tests in healthy subjects above 65 years of age, revealed a diabetic condition more frequently than in younger adults (aged below 60 years).

Moreover, bibliographic research did not reveal specific studies on diabetes in the oldest old group, only some epidemiological studies mention that the incidence of diabetes is lower in the centenarian population. Similar findings were also published in the Italian population (Carnazzo et al., 1996). Somehow higher values, but still lower compared to the general elderly population, were found in Danish centenarians (Andersen-Ranberg et al., 2001). However, with respect to the new diagnostic value, also in the Danish centenarians were found values as high as in the elderly population.

Therefore, the present study aims to evaluate the glycemic status in a wide group of centenarians, selected by epidemiological criteria, which might represent the general conditions of the Italian centenarian population.

2. Subjects and methods

Our population sample was composed by 602 centenarians ranging from 100 to 109 years (mean value = 101.1 ± 1.4). These subjects were enrolled from various regions of Italy. We selected, from a population of 14,274,591 inhabitants involved in the IMUSCE (1997) studies, 1,173 centenarians (202 males and 971 females). Out of 1,173 centenarians we sorted out 650 subjects, keeping the same frequency and gender ratio found along the different Italian regions. We have chosen 602 centenarians, which are representative of the general health conditions of centenarians in Italy.

The control sample was taken from the studies of the ILSA Group (1997), performed on a selected population of 4,528 elderly subjects ranging from 65 to 84 years, aiming at revealing the incidence of morbidity and mortality in the Italian population.

Both these studies were performed by using identical methods, applying rigorous epidemiological, clinical, methodological, complex biogerontological criteria, described in Maggi et al., 1994; IMUSCE, 1997. Concerning the total pool of subjects, a database was

created, containing the anagraphic and socio-economic data, as well as the familiar, physiological, remote and recent pathological, pharmacological anamnesis, physical examination, the psychometric scales values, Mini Mental State Examination (MMSE), Activity daily living (ADL), Instrumental activities of daily living (IADL), the routine and special laboratory results, using standardised methods and autoanalyzer technics (Motta et al., 2002). Plasma glucose was measured with glucose oxidase method. The study was carried out in absence of any acute illness.

Having considered all these data, we established the prevalence of diabetes based on WHO (1985) and WHO (1998) criteria. The individuals with diabetes were divided in 2 classes: Class 1 included those older than 65 years, diagnosed with diabetes in younger or medium ages, (< 60 years of age considered as long-lasting diabetes). Class 2 including individuals over 65 years with senile diabetes, diagnosed at the age > 65 years.

Significance was calculated by χ^2 by Yate's correction.

3. Results

As shown in Table 1, on the basis of the WHO (1985) criteria, 38 out of 602 centenarians (6.31 %) were considered affected by diabetes mellitus, while on the basis of WHO (1998) criteria, centenarians considered as diabetic were 46 (7.64 %). If we compare the data in Table 1, centenarians clearly display a lower significant prevalence of diabetes, when compared to younger elderly people, independently from the applied diagnostic criteria. All centenarians (100%) had type 2 diabetes.

If we considered the age at which the diabetes was diagnosed, centenarians appeared to be affected by senile diabetes (99.67%), with the only exception of 2 cases. The prevalence of senile diabetes in centenarians was 5.9 % by WHO criteria 1985) and 7.3 % by WHO criteria 1998,, while the long-lasting diabetes was only 0.33 % with both of the criteria used (Table 2). This means that diabetes in the centenarians is almost exclusively of senile type, while in the elderly people, the long-lasting diabetes is prevailing. The age of centenarian diabetics in which the disease was diagnosed, was 88 years in 1 case, and in all other cases were over 90 years (average: 99.6 years). Our data also show that the patients with diabetes diagnosed at the age of 88 years were in bad health conditions, suffering also by chronic-degenerative diseases.

Centenarians with neodiagnosed diabetes were 3.8 % out of the total group of centenarians, and represented the 60.5 % of the diabetic centenarians. As regards to the

therapy, 24.4 % of them were treated with oral antidiabetics, while only 2.2 % with insulin. Centenarians with diabetes were characterised by a specific clinical-metabolic situation, although with good haemato-clinical parameters. As a matter of fact, the great majority of them did not need any pharmacological therapy.

Our analyses revealed that among the 602 centenarians there were 2 subjects with diabetes cured 50 years with insulin therapy. They were in excellent clinical conditions, without cognitive disorders, without any considerable alterations at physical examination, with hematochemical parameters in the normal ranges. They do not show diabetic familiar history either. The only findings was hypoacusia, and an incipient cataract in one of them. They do not show any of the risk factors considered as signs of chronic-degenerative vascular complications. In spite of diabetes, they had normal blood pressure, they did not smoke, and performed a physical activity comparable to other non diabetic centenarians, they consumed an equilibrated diet and were modest drinkers (<150 ml/day) (Motta et al., 2002).

As far as the control sample is concerned, diabetic elderly subjects of 65-84 years of age were 594 (13.11 %) (according to WHO, 1985), and 684 (15.11 %) (according to WHO, 1998) (Table 1). These patients had almost exclusively type 2 diabetes (97.9 %). Most of them had long-lasting diabetes (73.4 % or 72.9% according to WHO, 1985 or WHO, 1998 respectively) and senile diabetes in 26.6 % or 27.1 % (according to WHO, 1985 or WHO, 1998, respectively) (Table 2). The neodiagnosed diabetes was only 0.28 % of the total population, and 1.87 % of the elderly with diabetes.

4. Discussion

Our clinical and laboratory data show in centenarians the symptoms of diabetes are less severe and the metabolic conditions are better, as compared to the healthy elderly people. This is demonstrated by the lower need of insulin therapy, and many other factors. Indeed, pharmacological treatments strongly depended on the period of the disease. We found that insulin treatment was prescribed in the 10.9 % of cases, (26.3 % for long-lasting diabetes) In previous studies these figures were 21.4 % for senile diabetes, and 54.7 % for long-lasting diabetes (Motta L. et al,1994).

This is related to the types of diabetes, in particular long-lasting diabetes which affect less frequently centenarians than healthy elderly people.

All these findings suggest that long-lasting diabetes is not compatible with the attainment of extreme longevity. Therefore, it is of great interest understand this phenomenon.

It has widely been shown that the evolution of the arteriosclerotic disease and the extent of the chronic-degenerative complications are correlated with the patient age, and with the duration of the diabete pathology (Rosso et al., 2001). These events may cause the breakdown of the unstable equilibrium of the long living subjects, and avoid the attainment of extreme longevity.

In general , the possibility to develop diabetes at advanced age depends more on the chronic-degenerative pathologies, frailty, reduced physical activity, malnutrition, infective components, insulin-resistance, adverse drug reactions, rather than on hereditary-familiar factors (Goldberg and Coon, 1994; Hedenmalm et al., 2002).

It is really difficult to explain how two subjects affected by long-lasting diabetes became healthy centenarians. It is hypothesised that possible unidetified protective factor(s) against the degenerative complications of the atherosclerosis, might exist (Rosso et al., 2001).

A further question is how the senile diabetes become clinically evident in long living people usually only after 90 years of age. A possible role for involutive processes, correlated to the pancreatic atherosclerosis, (Meneilly and Tessier, 1995; Puca and Perls, 2001). As a matter of fact, it has been shown that the pancreatic and generalized atherosclerotic lesions and the chronic-degenerative complications become progressively more severe 10 years later from the occurrence of diabetes (Rosso et al., 2001). These two considerations might justify why the diabetic elderly people with long-lasting diabetes usually do not become centenarians.

In conclusion, as it has been exposed above, the long-lasting diabetes, starting at around 60 years of age or earlier, usually do not allow to achieve 100 years of age. Indeed, diabetes occurs in the oldest old with a lower frequency than in the healthy elderly subjects (65-84 years), and it becomes clinically evident only after 90 years of age. Moreover, diabetes in the oldest old has usually few and silent symptoms, thus it is diagnosed very lately in life.

REFERENCES

- ADA (American Diabetes Association), 1997. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 20(7), 1183-1197.
- Alberti, K.G.M.M., Zimmet, P.Z., 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional Report of a WHO consultation. *Diabet. Med.* 15, 539-553.
- Andersen-Ranberg, K., Schroll, M., Jeune, B., 2001. Healthy centenarians do not exist, but autonomous centenarians do: a population-based study of morbidity among Danish centenarians. *J. Am. Geriatr. Soc.* 49, 900-908.
- Carnazzo, G., Rosso, D., Di Stefano, F., Corrao, G., Di Francesca, M., Motta, M. Giarelli, L., Bussani, R., Motta, L., 1996. On the pathogenesis of diabetes mellitus. *Diabete* 8, 67-77.
- Goldberg, A.P., Coon, P.J., 1994. Diabetes mellitus and glucose metabolism in the elderly. In: Hazzard. W.R. (Eds): *Textbook Principles of Geriatric Medicine and Gerontology*. McGraw-Hill, New York, pp. 845-868.
- Hedenmalm, K., Hagg, S., Stahl, M., Mortimer, O., Spigset, O., 2002. Glucose intolerance with atypical antipsychotics. *Drug Safety* 25, 1107-1116.
- IDF, 2007. Diabetes Prevalence at <http://www.idf.org/home/index.cfm?node=264>
- ILSA Group (The Italian Longitudinal Study on Aging Working Group), 1997. Prevalence of chronic diseases in older Italians: comparing self-reported and clinical diagnoses. *Int. J. Epidemiol.* 26, 995-1002.
- IMUSCE (The Italian Multicenter Study on Centenarians), 1997. Epidemiological and socioeconomic aspects of Italian centenarians. *Arch. Gerontol. Geriatr.* 25, 149-157.
- Laaksonen DE, Lindstrom J, Lakka TA, Eriksson JG, Niskanen L, Wikstrom K, Aunola S, Keinanen-Kiukaanniemi S, Laakso M, Valle TT, Ilanne-Parikka P, Louheranta A, Hamalainen H, Rastas M, Salminen V, Cepaitis Z, Hakumaki M, Kaikkonen H, Harkonen P, Sundvall J, Tuomilehto J, Uusitupa M; Finnish diabetes prevention study, 2005. Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. *Diabetes* 54(1):158-165.
- Maggi, S., Zucchetto, M., Grigoletto, F., Baldereschi, M., Candelise, L., Scarpini, E., Scarlato, G., Amaducci, L., 1994. The Italian Longitudinal Study on Aging (ILSA): Design and methods. *Ageing* 6, 464-472.
- Meneilly, G.S., Tessier, D., 1995. Diabetes in the elderly. *Diabetic Medicine* 12, 949-960.

- Meneilly, G.S., Tessier, D., 2001. Diabetes in elderly adults. *J. Gerontol. A. Biol. Sci. Med. Sci.* 56, M5-M13.
- Miggiano GA, Gagliardi L, 2006. Diabetes and Diet revisited. *Clin Ter* 157(5); 443-455. Review. Italian.
- Motta L, Carnazzo G.,1994. Il Diabete nell'anziano. 95° Congresso Soc. Ital. Medicina Interna. Ed. L. Pozzi, Roma, 31-37.
- Motta, M., Maugeri, D., Malaguarnera, M. and IMUSCE, 2002. Centenarians in good health conditions. *Arch. Gerontol. Geriatr. Suppl.* 5, 209-217.
- No authors listed, 1979. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes.* 28(12):1039-1057.
- Puca, A., Perls, T., 2001. Centagenetix, Inc. Boston, USA; Gerontology Division, Beth Israel Deaconess Medical Center and Division on Aging; Harvard Medical School, Boston, USA. *Giorn. Gerontol.* 49, 861-869 (Italian).
- Rosso, D., Carnazzo, G., Giarelli, L., Motta, L., Maugeri, D., 2001. Atherosclerosis and pancreatic damage. *Arch. Gerontol. Geriatr.* 32, 95-100.
- Stolk, R.P., Pols, H.A., Lamberts, S.W., De Jong, P.T., Hofman, A., Grobbee, D.E., 1997. Diabetes mellitus, impaired glucose tolerance, and hyperinsulinemia in an elderly population. The Rotterdam Study. *Am. J. Epidemiol.* 145, 24-32.
- Uusitupa M, Louheranta A, Lindstrom J, Valle T, Sundvall J, Eriksson J, Tuomilehto J. The Finnish Diabetes Prevention Study, 2000. *Br J Nutr.* 83 Suppl 1:S137-42.
- WHO (World Health Organization), 1982. ICD 9 CM International Classification of Disease. Ninth Revision Geneva, WHO Publication.
- WHO (World Health Organization), 1985. Diabetes Mellitus Report of WHO Study Group. Geneva WHO Techn. Rep. Ser. N. 727.
- Wilson, P.W., Anderson, K.M., Kannel, W.B., 1986. Epidemiology of diabetes mellitus in the elderly. The Framingham Study. *Am. J. Med.* 16,80(5A), 3-9.

****Appendix 1.**

The Italian Multicenter Study on Centenarians (IMUSCE)

Coordinators: M. Motta, C. Franceschi, L. Motta

List of participants of IMUSCE:

Universities:

University of Bari: A. Capurso, F. Panza, V. Solfrizzi, A. D'Introno,

A.M. Colacicco, S. Capurso

University of Bologna: M. Capri, S. Salvioli, S. Valensin.

University of Catania: M. Malaguarnera,

E. Bennati, L. Ferlito, A. Franzone, R. Rapisarda

University of Cosenza: G. De Benedictis, M. Berardelli

University of Firenze : G. Masotti, E. Petrucci, I. Petrucci, P. Pinzani, F. Mantelacchi, M.

Pazzagli, F.M. Antonini

University of Foggia: C. Capurso

University of Messina: V. Nicita-Mauro, C. Lo Balbo, A. Mento, C. Nicita-Mauro, G.

Maltese, G. Basile

University of Milano: D. Mari, R. Coppola, R. Provenzano

University of Modena: G. Salvioli, M.V. Baldelli, C. Mussi

University of Napoli : M. Varricchio, M. Barbieri, A. Gambardella, G. Paolisso

University of Palermo: C. Caruso, G. Candore, G. Colonna-Romano, D. Lio

University of Parma: P. Sansoni, R. Vescovini, C. Biasini, F. Zanni, L. Zanlari,

A. Telera, G. Lucchini, G. Passeri, M. Passeri

University of Pavia: E. Ferrari, L. Cravello, L. Barili., S.B. Solerte, M. Fioravanti,

F. Magri, F. Fagnoni

University of Perugia: U. Senin, P. Mecocci, A. Cherubini

University of Roma "La Sapienza": V. Marigliano, L. Tafaro, P. Cicconetti,

F. Tombesi, M.T. Tombolillo, E. Ettore

University of Siena : S. Forconi, S. Boschi, G.A. Righi, M. Guerrini

University of Trieste: L. Giarelli[†], G. Stanta

Other institutions and specialists:

National Institute on Aging, National Institutes of Health, Baltimore, Bethesda, MD (USA):

L. Ferrucci, A. Ble, EJ. Metter, J M. Guralnik

Istituto Superiore di Sanità, Department of Pharmaca, Roma: R. Pacifici,

P. Zuccaro, I. Palmi

Local Sanitary Unit No.3, Operative Unit of Geriatrics, Acireale (CT): S. Branca, M.

Passamonte, M. P. Gargante, C. Risino

Local Sanitary Unit No.6, Azienda Ospedaliera dei Bianchi, Corleone (PA):

G. Fradà.

Physiotherapist: F. Motta

Laboratory technician: G. Crimi

All the listed participants of this study have contributed to the identification of cases, elaboration and compilation of the clinical records, to collection and evaluation of the data, therefore, the present work is the result of an intense collegial activity. We declare that all participants of IMUSCE have equal merits in all parts of this work.

Table 1. The prevalence of diabetes in 602 centenarians and 4528 elderly (65-84 years)

Diagnostic criteria	Elderly		Centenarians		P
	Diabetes		No Diabetes		
	N	%	N	%	
WHO 1985 (Diabetes FPG ≥140 mg/dl)	594 (13.11%)	3934 (86.89%)	38 (6.31%)	564 (93.69%)	< 0.004
WHO 1998 (Diabetes FPG ≥126 mg/dl)	684 (15.11%)	3844 (84.89%)	46 (7.64%)	556 (92.36%)	< 0.001

Table 2. The prevalence (%) of senile and long-lasting diabetes in 602 centenarians and 4528 elderly

Groups of subjects	Criteria applied	Diabetes	Senile diabetes	Long-lasting diabetes
Centenarians	WHO (1985)	5.90	99.67	0.33
	WHO (1998)	7.30	99.67	0.33
Elderly	WHO (1985)	13.11	26.60	73.40
	WHO (1998)	15.11	27.10	72.90

Senile diabetes – diagnosed at 65 years and over

Long-lasting diabetes – diagnosed at a younger and middle-age

Table 3. Therapy in centenarians with diabetes

Type of therapy	% of diabetics
Diet +Oral antidiabetics	24.40
Diet +Insulin therapy	2.20
Only Diet	12.90
New diagnosed (no specific therapy)	60.50