MINIREVIEWS

Impact of glucose level on morbidity and mortality in elderly with diabetes and pre-diabetes

Orit Twito, Meir Frankel, Dan Nabriski

Orit Twito, Meir Frankel, Dan Nabriski, Endocrinology, Diabetes and Metabolism Institute, Meir Medical Center, Kfar Saba 44281, Israel

Author contributions: Twito O proposed the initial idea of the paper, wrote part of the paper and read and approved the final manuscript; Frankel M wrote part of the paper, and read and approved the final manuscript; Nabriski D made critical revisions, and read and approved the final manuscript.

Conflict-of-interest: The authors declare that they have no competing interests.

Correspondence to: Dr. Orit Twito, Endocrinology, Diabetes and Metabolism Institute, Meir Medical Center, 59 Tschernihovsky, St., Kfar Saba 44281, Israel. orit.twito@clalit.org.il
Telephone: +972-9-7472788
Fax: +972-9-7471644

Abstract

The prevalence of type 2 diabetes mellitus (DM) increases with age and reaches 25% in those older than age 65 years. Pre-diabetes status is also very common in the elderly, and is present in about half of those age 75 years and older. Many physicians care for elderly patients with diabetes and pre-diabetes, dealing with the challenge of controlling glucose levels and improving health with minimal adverse events. Over the last decade, research on diabetes among the elderly population has proliferated, adding new information on this topic. This review summarizes the updated medical literature on diabetes and pre-diabetes in the elderly, including the significance of pre-diabetic conditions, new-onset DM in the elderly and long-standing DM. The role of therapeutic intervention and the level of glycemic control for this population are discussed in particular.

Key words: Diabetes mellitus; Elderly; Old age; Pre-diabetes; Glycemic control

Core tip: The prevalence of diabetes mellitus (DM) and pre-diabetes in old age is very high. However, clinical guidelines do not provide complete information to the clinician managing patients with these conditions. Pre-diabetes status in the elderly increases the risk for DM, but probably does not increase the risk of cardiovascular morbidity and mortality. The role of therapeutic interventions in elderly patients with pre-diabetes is not yet proven. New-onset DM in older age is associated with better glycemic control and better prognosis compared to long standing DM in this population. Nevertheless, higher glucose levels in elderly with new-onset DM are associated with increased all-cause mortality. The benefits of tight glycemic control in elderly with long standing DM are doubtful and may cause more harm than good. To conclude, more research in this field is needed. Currently, the clinical approach for DM and pre-diabetes in the elderly should be tailored to meet individual needs.

Twito O, Frankel M, Nabriski D. Impact of glucose level on morbidity and mortality in elderly with diabetes and pre-diabetes. *World J Diabetes* 2015; 6(2): 345-351 Available from: URL:

INTRODUCTION

The concept of individualized treatment for type 2 diabetes mellitus (DM) is becoming established and replaces previous recommendations for tight glucose control for all diabetic patients. One of the main criteria in constructing personalized care for the patient is the chronologic and biologic age.

The incidence and prevalence of DM increase with age (www.cdc.gov/diabetes/statistics). Pre-diabetes states, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and elevated HbA1c are even more prevalent among the elderly[1-3].

However, the clinical impact of glucose levels on microvascular and macrovascular complications, and mortality is not well established. The commonly used clinical guidelines do not provide separate recommendations for elderly individuals with pre-diabetes, and do not differentiate between elderly with long-standing or new-onset DM[4].

This review summarizes the data in the literature regarding the effect of glycemia in different stages on morbidity and mortality in the elderly population. It will address the aspects of the clinical impact of glucose levels in pre-diabetes, diabetes that was first diagnosed in old age and long-standing diabetes separately.

PRE-DIABETES IN THE ELDERLY

According to American Diabetes Association (ADA) guidelines, pre-diabetes may be diagnosed as IFG, IGT and/or by elevated HbA1c values of 5.7%-6.4%[4]. The rates of pre-diabetes states, including IFG and IGT, are very common in the general population, and increase with age[1-3].

It is well-established that pre-diabetes states are a significant risk factor for developing type 2 DM, as well as for diabetic complications and mortality in younger adults[5,6]. It is also well known that lifestyle changes, including loss of at least 7% of body weight and $\geq$ 150 min/wk of activity, delay or even prevent development of DM, and may potentially reduce its complications among persons with pre-diabetes[7]. Thus, pre-diabetic patients are an important target group for primary prevention interventions.

Understanding the clinical impact of pre-diabetes in older adults is very important, as the prevalence of pre-diabetes increases with age and reaches about 50% in those age 75 years and older[2]. Moreover, lifestyle interventions are more successful in decreasing hyperglycemia in the elderly than in younger adults. This was demonstrated in the Diabetes Prevention Program (DPP) trial, which included subjects with combinations of IGT and IFG, considered to be at high risk for developing DM. The oldest age group, 60-85 years at enrollment, had the greatest benefit from the program, both in terms of weight loss and decreased incidence of DM over time[7,8].

Yet, there are some important, unanswered questions for the clinician. First, what is the clinical impact of pre-diabetes state in the elderly? Second, do glucose lowering interventions improve morbidity and mortality in this population?

The answer to the first question, regarding the clinical significance of pre-diabetes in elderly subjects, is based on a small number of studies (Table 1). A prospective, observational study followed 1466 elderly subjects with IGT and compared their mortality rate to subjects with normal glucose levels and overt diabetes. The age of enrolled participants was 55-74 years and median follow-up was 8.8 years. Mortality rates were almost equal in the pre-diabetes and normal glucose groups. Nevertheless, within the non-diabetic range (*i.e.*, normal and pre-diabetic glucose levels), a J-shaped association was demonstrated between glycemia and all-cause mortality, even after adjustment for multiple risk factors. The lowest mortality rates were documented in subjects with fasting plasma glucose 88-93 mg/dL and HbA1c 5.4%-5.5%. Participants with glucose levels at the upper pre-diabetes range had a higher mortality rate[9].

On the other hand, a recent prospective cohort study of 8365 older subjects, 50-74 years old, revealed that the increased cardiovascular risk in pre-diabetes (defined as IFG or HbA1c 5.7%-6.4%) can mainly be explained by other concurrent cardiovascular risk factors and not by the hyperglycemia itself[10]. Similar results arose from the Cardiovascular Health Study of 4602 community-dwelling elderly participants, 65 years-of-age and older. This study found no evidence that pre-diabetes is an independent risk factor for a variety of cardiovascular outcomes, including heart failure, myocardial infarction, stroke and all-cause mortality[11]. Pre-diabetes increased the risk of developing DM, but the absolute rate was low and not related to increased cardiovascular risk.

An interesting pooled analysis examined the age specific effect of different metabolic risk factors on cardiovascular diseases. The analysis for plasma glucose included 372000 participants in 116 cohorts. The authors calculated the impact of mildly elevated glucose on the relative risk of ischemic heart disease and stroke. They concluded that the proportional effect of elevated fasting glucose declined with age[12].

For the second question - whether glucose lowering intervention would improve morbidity and mortality outcomes in elderly population - there is still no satisfactory answer. The DPP study, mentioned above, found a better response of elderly subjects to lifestyle interventions, in particular weight loss and DM prevention. However, clinical outcome data were not reported[7,8]. The effect of lifestyle

Table 1 Studies comparing cardiovascular morbidity and mortality in elderly with pre-diabetes and normal glucose tolerance

Ref.	No. of participants	Age at inclusion	Length of follow up (yr)	Population	Results
Kowall *et al*[9]	1466	55-74	8.8 (median)	German	Mortality rates were almost equal in the pre-diabetes and NGT groups
Schöttker *et al*[10]	8365	50-74	7.9 (median)	German	Major CV event[1] rates were almost equal in the pre-diabetes and NGT groups
Deedwania *et al*[11]	4602	≥ 65	13 (median)	United States: 87% Caucasians, 13% African American	Major CV event[2] rates were almost equal in the pre-diabetes and NGT groups

[1]Major cardiovascular events including non-fatal stroke, non-fatal MI and cardiovascular mortality; [2]Major cardiovascular events including heart failure, MI, angina pectoris, stroke and all-cause mortality. CV: Cardiovascular; NGT: Normal glucose tolerance; MI: Myocardial infarction.

interventions on mortality and cardiovascular disease in pre-diabetes patients is questionable, even among younger adults[13].

In summary, existing data regarding the clinical impact of pre-diabetes on morbidity and mortality among elderly individuals are limited and study results are conflicting. There is an association between pre-diabetes and mortality, which increases with higher glucose levels within the pre-diabetic range. However, it is unclear whether pre-diabetes is a marker of poor metabolic condition or an independent risk factor. There is almost no information regarding the influence of lifestyle or medical interventions on morbidity and mortality in this population.

The ADA does not have separate clinical guidelines for pre-diabetes in the elderly population[4]. The 2012 consensus report of the ADA and the American Geriatrics Society provided vague advice on this issue. They recommended screening for pre-diabetes in elderly patients who are likely to benefit from diagnosis of pre-diabetes and from subsequent intervention. Similarly, they recommended lifestyle interventions for elderly individuals with pre-diabetes who are able to participate and are likely to benefit from DM prevention[14].

NEW-ONSET DIABETES IN THE ELDERLY

The pathophysiology of the appearance of DM in the elderly is a combination of age-related changes in carbohydrate metabolism, pancreatic endocrine dysfunction and adverse lifestyle factors[15,16]. The epidemiology of incident DM in relation to population age is interesting. The incidence of new-onset DM increases with age until age 65 years, after which both incidence and prevalence of DM seem to level off (www.cdc.gov/diabetes/statistics).

The natural history of new-onset DM in the elderly seems to have a benign course in comparison to that of long-standing DM. Interesting information comes up from a study of centenarian subjects, ages 100-109, compared to elderly subjects aged 65-84 years. The centenarians had relatively low prevalence of DM (7.64%), and almost exclusively had senile DM, that is DM diagnosed after 65 years of age. The authors suggest that long-standing DM is not compatible with extreme longevity, while senile DM does not change the clinical outcomes significantly[17]. New onset DM in older age is associated with better glycemic control[18] and with less frequent microvascular complications compared to long standing DM[19]. Data from the National Health and Nutrition Examination Survey database found that although elderly with new-onset DM were 5 years older in average, they had much lower prevalence of retinopathy and a similar burden of macrovascular disease compared with long-standing DM. The difference in retinopathy rate may reflect the difference in DM duration between the two groups[20].

The few studies that compared elderly subjects with new-onset DM to non-diabetic patients demonstrated short term elevation in all-cause and cardiovascular mortality and long term elevation of microvascular and macrovascular complications[21-25]. None of these studies checked the association of glucose levels with mortality or diabetic complications and did not consider the influence of other cardiovascular risk factors on morbidity and mortality.

A large, observational study focused on the association between glycemic control and mortality in elderly patients with new-onset DM. This study followed almost 3000 elderly patients with new-onset DM for 7 years. A J-shaped relationship was found between HbA1c level and mortality rate. A HbA1c level above 7.5% was associated with significantly higher all-cause mortality, while the lowest mortality rate was found in subjects with HbA1c levels from 6.5% to 6.99%. This association remained statistically significant after adjustment for other conventional cardiovascular risk factors[26].

In summary, the existing data suggest that new-onset DM in the elderly is associated with better glycemic control and better prognosis compared to long-standing DM in this population. However, when compared to elderly people with normal glucose levels, the new-onset DM patients have higher rates of morbidity and mortality (Table 2). There is some evidence that higher glucose levels within the diabetic range are associated with increased mortality.

The ADA guidelines do not deal separately with new-onset DM in elderly individuals, but mention the

Table 2 Studies comparing cardiovascular morbidity and mortality in elderly subjects with new-onset diabetes mellitus and subjects with normal glucose tolerance and long-standing diabetes mellitus

Ref.	No. of participants	Glycemic status	Age at inclusion(yr)	Length of follow up (yr)	Population	Results
Wang *et al*[19]	155	New-onset DM and long-standing DM	≥ 65	-	China	Microvascular complication rate was higher in long-standing DM
Selvin *et al*[20]	2809	New-onset DM and long-standing DM	≥ 65	-	United States	Microvascular complication rate was higher in long-standing DM
Smith *et al*[21]	1119	NGT and new-onset DM	≥ 65	5.9 (median)	United States	Mortality rate was higher in new-onset DM
Bethel *et al*[22]	59335	NGT and new-onset DM	≥ 65	10 (median)	United States	Microvascular and macrovascular complication rates were higher in new-onset-DM
Panzram *et al*[23]	2381	New-onset DM	All	10 (median)	German	Mortality rate was related to age of onset of DM and was higher in men
Croxson *et al*[24]	861	NGT, IGT, new-onset DM and long-standing DM	65-85	4.5 (median)	United Kingdom	New onset DM was associated with increased mortality
Tan *et al*[25]	10782	NGT and new-onset DM	≥ 65	4.6 (median)	Scotland	New onset DM was associated with increased mortality in females
Twito *et al*[26]	2994	New-onset DM	≥ 65	5.5 (mean)	Israel	Mortality rates in new-onset DM were associated with HbA1c levels

NGT: Normal glucose tolerance; IGT: Impaired glucose tolerance; DM: Diabetes mellitus.

duration of the disease as a parameter that should be considered when choosing HbA1c target levels[4]. Vacante *et al*[27] suggested combining the current age of the patient with the duration of DM.

LONG-STANDING DIABETES IN THE ELDERLY

As mentioned above, long-standing DM in the elderly has higher morbidity rates compared to new-onset DM. Therefore, the question is whether good glycemic control in elderly people with long-standing DM will influence the course of the disease.

In young and middle-aged diabetic patients, the role of tight glycemic control is crucial, as was proven in the Diabetes Control and Complications Study (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) in type 1 and type 2 DM, respectively[28-30]. These two studies confirmed the benefit of intensive glycemic control in reducing microvascular and macrovascular complications[31]. Nonetheless, these studies included only new-onset diabetic patients and excluded patients ages 65 years and above at the time of enrollment.

Almost 10 years after the publication of the UKPDS study, and 15 years after the DCCT study, 3 large randomized controlled trials examined the influence of intensive glycemic control on microvascular and macrovascular complications in older subjects with long standing DM. The Action to Control Cardiovascular Risk in Diabetes trial[32] enrolled diabetic patients (mean age 62.2 ± 6.8 years) 10 years after diagnosis, 35% with previous cardiovascular disease. This trial was terminated after 3 years because of excessive deaths in the intensive glycemic control arm. The Action in Diabetes and Vascular Disease trial[33], which had also enrolled people with advanced disease (mean age 66 ± 6 years, average duration of diabetes 8 years, 32% with previous major macrovascular disease), showed no significant effect of tight glycemic control on major macrovascular events or death from any cause, but there was significant reduction in nephropathy incidence and as a result, reduction in the incidence of combined microvascular and macrovascular events. This reduction was proven only for patients younger than 65 years, according to a sub-group analysis published as part of the trial. The Veterans Affairs Diabetes Trial trial[34] enrolled similar diabetic patients (mean age 60.5 ± 9 years, 11.5 years after diagnosis, 41% with major macrovascular disease) and also showed no significant effect of tight glycemic control on major macrovascular events or death from any cause. As one would expect, adverse events related to intensive glycemic control, such as hypoglycemia, were more common in the elderly[35].

Few studies are directed to glycemic control in the old age. For example, the retrospective diabetes and aging study[36] enrolled participants above 60 years of age (38% between 70-79 years and 15% age 80 or older); 57% had diabetes for more than 4 years at enrollment. There was a U-shaped relationship between

Table 3 Studies on the role of tight glycemic control in long-standing diabetes mellitus

Study	No. participants	Years since diagnosis	Mean age at enrollment (yr)	Length of follow up (yr)	Population	Results
ACCORD trial[32]	10251	10 (median)	62.2 ± 6.8	3.4 (median)	United States and Canada	Terminated after 3.5 yr; excessive deaths in the intensive glycemic control arm
ADVANCE trial[33]	11140	8 (mean)	66 ± 6	5 (median)	Asia, Australasia, Europe, and North America (20 countries)	No significant effect of tight glycemic control on major macrovascular events or death; significant reduction in nephropathy incidence
VADT trial[34]	1791	11.5 (mean)	60.5 ± 9	5.6 (median)	United States military veterans; 97% males	No significant effect of tight glycemic control on major macrovascular events or death
Diabetes and aging study[36]	71092	8.3 (mean)	71 ± 7.4	3.1 (mean)	California, United States	U-shape relationship between mortality and HbA1c, with the lowest mortality rate at HbA1c 6%-8%

ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease; VADT: Veterans Affairs Diabetes Trial.

mortality and HbA1c, with the lowest mortality rate at HbA1c 6%-8%, in all age-groups (Table 3).

The benefit of tight glycemic control for prevention of microvascular complications is not immediate. As proven in the UKPDS studies, the difference in outcome between the tight glycemic control group and the control group only appeared 9 years after randomization[14,31]. In other words, for patients with life expectancy of 7 years or less, the benefit in this area is doubtful.

The complexities of diabetes care in old age, with benefits alongside potentially serious adverse events, led researchers to quality-adjusted life year (QALY) trials. Vijan *et al*[37] compared the QALY gained with intensive glycemic control versus moderate glycemic control, in different age-groups. They concluded that older patients, age 75 years and older, experience smaller benefit from glycemic control compared to younger patients, and their expected gain in QALYs for a 1-point change in HbA1c was minimal, even with the favorable assumption that the benefits of glycemic control extend to the elderly.

The results of the aforementioned studies resulted in changes in the clinical guidelines regarding treatment goals for elderly with long-standing DM. However, the guidelines offer general instructions and leave a large margin for clinical judgment.

The 2014 ADA guidelines[4] recommend a standard glycemic goal of HbA1c below 7% for adults, and a less stringent goal, such as < 8% for patients with a more complex status, which is defined according to disease duration, life expectancy, important comorbidities, risk for adverse events and existing vascular complications. The International Association of Gerontology and Geriatrics and the European Diabetes Working Party for Older People published similar recommendations[38].

The consensus report of the ADA and the American Geriatrics Society from 2012[14], offered 3 levels of glycemic control for the old patient: HbA1c < 7.5% for healthy patients, < 8% for patients with intermediate health status (multiple chronic illnesses, 2+ instrumental impairments or mild cognitive impairment), and < 8.5% for patients with poor health status (end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ activities of daily living dependencies). The International Diabetes Federation 2013 guidelines[39], suggest a similar categorization. They also emphasize that for end-of-life situations, the goal should be merely to avoid symptomatic hyperglycemia (Table 4).

CONCLUSION

This review summarizes the current evidence about glycemic control in the elderly. Similar to young and middle-aged adults with DM, it seems that the elderly patient with diabetes has higher risks for morbidity and mortality compared to a non-diabetic person of the same age. Even so, new-onset DM is less severe in elderly patients compared to young adults and easier to control. The impact of pre-diabetes state on morbidity and mortality risk in the elderly is doubtful, and the role of screening and treatment in these patients is questionable. Finally, the importance of tight glycemic control on long-standing DM in the elderly in not well-established and the preferred level of glycemic control among elderly patient subgroups requires

Table 4 Guideline recommendations for glycemic control in the elderly

Article	Age	HbA1c target	Population
The 2014 ADA guidelines[4]	Any age	< 7%	Adult patients without serious comorbidities
		< 8%	Patients with a more complex status (see text)
			Age itself not a criteria
The consensus report of the ADA and the American Geriatrics Society 2012[14]	> 65 yr	< 7.5%	Healthy old patients
		< 8%	Patients with intermediate health status (multiple chronic illnesses or 2+ instrumental impairments or mild cognitive impairment)
		< 8.5%	Patients with poor health status (end-stage chronic illnesses or moderate to severe cognitive impairment or 2+ ADL dependencies)
The 2013 IDF guidelines[39]	> 70 yr	7%-7.5%	Functionally independent old patients
		7%-8%	Functionally dependent old patients
		< 8.5%	Frail elderly or dementia
		Any HbA1c; just to avoid hypoglycemia	Patients at end-of-life

ADA: American Diabetes Association; ADL: Activities of daily living; IDF: International Diabetes Federation.

further evaluation.

Beyond all the above, the heterogeneity of the elderly population presents a significant challenge in clinical decision making. Old diabetic patients can be healthy or with much comorbidity and the risks of adverse events from medications increases with age. The decision regarding an individual patient's glycemic goal should be made, ideally with the patient himself, after considering all the comorbidities, together with current cognitive state, risk of adverse events, quality of life aspects and life expectancy.

ACKNOWLEDGMENTS

REFERENCES

1 **Karve A**, Hayward RA. Prevalence, diagnosis, and treatment of impaired fasting glucose and impaired glucose tolerance in nondiabetic US adults. *Diabetes Care* 2010; **33**: 2355-2359 [PMID: 20724649 DOI: 10.2337/dc09-1957]

2 **Cowie CC**, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, Williams DE, Gregg EW, Bainbridge KE, Saydah SH, Geiss LS. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care* 2009; **32**: 287-294 [PMID: 19017771 DOI: 10.2337/dc08-1296]

3 **Mainous AG 3rd**, Tanner RJ, Baker R, Zayas CE, Harle CA. Prevalence of prediabetes in England from 2003 to 2011: population-based, cross-sectional study. *BMJ Open* 2014; **4**: e005002 [PMID: 24913327 DOI: 10.1136/bmjopen-2014-005002]

4 **American Diabetes Association**. Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]

5 **Selvin E**, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010; **362**: 800-811 [PMID: 20200384 DOI: 10.1056/NEJMoa0908359]

6 **Coutinho M**, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999; **22**: 233-240 [PMID: 10333939 DOI: 10.2337/diacare.22.2.233]

7 **Knowler WC**, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; **374**: 1677-1686 [PMID: 19878986 DOI: 10.1016/S0140-6736(09)61457-4]

8 **Diabetes Prevention Program Research Group**, Crandall J, Schade D, Ma Y, Fujimoto WY, Barrett-Connor E, Fowler S, Dagogo-Jack S, Andres R. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 1075-1081 [PMID: 17077202 DOI: 10.1093/gerona/61.10.1075]

9 **Kowall B**, Rathmann W, Heier M, Giani G, Peters A, Thorand B, Huth C, Icks A, Meisinger C. Categories of glucose tolerance and continuous glycemic measures and mortality. *Eur J Epidemiol* 2011; **26**: 637-645 [PMID: 21785986 DOI: 10.1007/s10654-011-9609-y]

10 **Schöttker B**, Müller H, Rothenbacher D, Brenner H. Fasting plasma glucose and HbA1c in cardiovascular risk prediction: a sex-specific comparison in individuals without diabetes mellitus. *Diabetologia* 2013; **56**: 92-100 [PMID: 22986731 DOI: 10.1007/s00125-012-2707-x]

11 **Deedwania P**, Patel K, Fonarow GC, Desai RV, Zhang Y, Feller MA, Ovalle F, Love TE, Aban IB, Mujib M, Ahmed MI, Anker SD, Ahmed A. Prediabetes is not an independent risk factor for incident heart failure, other cardiovascular events or mortality in older adults: findings from a population-based cohort study. *Int J Cardiol* 2013; **168**: 3616-3622 [PMID: 23731526 DOI: 10.1016/j.ijcard.2013.05.038]

12 **Singh GM**, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, Kaptoge S, Whitlock G, Qiao Q, Lewington S, Di Angelantonio E, Vander Hoorn S, Lawes CM, Ali MK, Mozaffarian D, Ezzati M. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One* 2013; **8**: e65174 [PMID: 23935815 DOI: 10.1371/journal.pone.0065174]

13 **Hopper I**, Billah B, Skiba M, Krum H. Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of randomised controlled clinical trials. *Eur J Cardiovasc Prev Rehabil* 2011; **18**: 813-823 [PMID: 21878448 DOI: 10.1177/1741826711421687]

14 **Sue Kirkman M**, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, Huang ES, Korytkowski MT, Munshi MN, Odegard PS, Pratley RE, Swift CS; Consensus Development Conference on Diabetes and Older Adults. Diabetes in older adults: a consensus report. *J Am Geriatr Soc* 2012; **60**: 2342-2356 [PMID: 23106132 DOI: 10.1111/jgs.12035]

15 **Meneilly GS**. Pathophysiology of type 2 diabetes in the elderly. *Clin Geriatr Med* 1999; **15**: 239-253 [PMID: 10339631]

16 **Mozaffarian D**, Kamineni A, Carnethon M, Djoussé L, Mukamal

KJ, Siscovick D. Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. *Arch Intern Med* 2009; **169**: 798-807 [PMID: 19398692 DOI: 10.1001/archinternmed.2009.21]

17 **Motta M**, Bennati E, Capri M, Ferlito L, Malaguarnera M. Diabetes mellitus in the extreme longevity. *Exp Gerontol* 2008; **43**: 102-105 [PMID: 17689906 DOI: 10.1016/j.exger.2007.06.012]

18 **Berkowitz SA**, Meigs JB, Wexler DJ. Age at type 2 diabetes onset and glycaemic control: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2010. *Diabetologia* 2013; **56**: 2593-2600 [PMID: 23995472 DOI: 10.1007/s00125-013-3036-4]

19 **Wang Y**, Qin MZ, Liu Q, Liu Q, Chang ZW. Clinical analysis of elderly patients with elderly-onset type 2 diabetes mellitus in China: assessment of appropriate therapy. *J Int Med Res* 2010; **38**: 1134-1141 [PMID: 20819452 DOI: 10.1177/147323001003800342]

20 **Selvin E**, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the u.s. *Diabetes Care* 2006; **29**: 2415-2419 [PMID: 17065677]

21 **Smith NL**, Barzilay JI, Kronmal R, Lumley T, Enquobahrie D, Psaty BM. New-onset diabetes and risk of all-cause and cardio-vascular mortality: the Cardiovascular Health Study. *Diabetes Care* 2006; **29**: 2012-2017 [PMID: 16936145 DOI: 10.2337/dc06-0574]

22 **Bethel MA**, Sloan FA, Belsky D, Feinglos MN. Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. *Arch Intern Med* 2007; **167**: 921-927 [PMID: 17502533 DOI: 10.1001/archinte.167.9.921]

23 **Panzram G**, Zabel-Langhennig R. Prognosis of diabetes mellitus in a geographically defined population. *Diabetologia* 1981; **20**: 587-591 [PMID: 7262474 DOI: 10.1007/BF00257424]

24 **Croxson SC**, Price DE, Burden M, Jagger C, Burden AC. The mortality of elderly people with diabetes. *Diabet Med* 1994; **11**: 250-252 [PMID: 8033522 DOI: 10.1111/j.1464-5491.1994.tb00267.x]

25 **Tan HH**, McAlpine RR, James P, Thompson P, McMurdo ME, Morris AD, Evans JM. Diagnosis of type 2 diabetes at an older age: effect on mortality in men and women. *Diabetes Care* 2004; **27**: 2797-2799 [PMID: 15562187 DOI: 10.2337/diacare.27.12.2797]

26 **Twito O**, Ahron E, Jaffe A, Afek S, Cohen E, Granek-Catarivas M, Klein P, Hermoni D. New-onset diabetes in elderly subjects: association between HbA1c levels, mortality, and coronary revascularization. *Diabetes Care* 2013; **36**: 3425-3429 [PMID: 23877985 DOI: 10.2337/dc12-2503]

27 **Vacante M**, Malaguarnera M, Motta M. Revision of the ADA-classification of diabetes mellitus type 2 (DMT2): the importance of maturity onset diabetes (MOD), and senile diabetes (DS). *Arch Gerontol Geriatr* 2011; **53**: 113-119 [PMID: 20800300 DOI: 10.1016/j.archger.2010.06.017]

28 The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; **329**: 977-986 [PMID: 8366922]

29 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 837-853 [PMID: 9742976 DOI: 10.1016/S0140-6736(98)07019-6]

30 Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 854-865 [PMID: 9742977 DOI: 10.1016/S0140-6736(98)07037-8]

31 **Holman RR**, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**: 1577-1589 [PMID: 18784090 DOI: 10.1056/NEJMoa0806470]

32 **Gerstein HC**, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545-2559 [PMID: 18539917 DOI: 10.1056/NEJMoa0802743]

33 **ADVANCE Collaborative Group**; Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560-2572 [PMID: 18539916 DOI: 10.1056/NEJMoa0802987]

34 **Duckworth W**, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129-139 [PMID: 19092145 DOI: 10.1056/NEJMoa0808431]

35 **Miller ME**, Bonds DE, Gerstein HC, Seaquist ER, Bergenstal RM, Calles-Escandon J, Childress RD, Craven TE, Cuddihy RM, Dailey G, Feinglos MN, Ismail-Beigi F, Largay JF, O'Connor PJ, Paul T, Savage PJ, Schubart UK, Sood A, Genuth S. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* 2010; **340**: b5444 [PMID: 20061360 DOI: 10.1136/bmj.b5444]

36 **Huang ES**, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. *Diabetes Care* 2011; **34**: 1329-1336 [PMID: 21505211 DOI: 10.2337/dc10-2377]

37 **Vijan S**, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. *JAMA Intern Med* 2014; **174**: 1227-1234 [PMID: 24979148 DOI: 10.1001/jamainternmed.2014.2894]

38 **Sinclair A**, Morley JE, Rodriguez-Mañas L, Paolisso G, Bayer T, Zeyfang A, Bourdel-Marchasson I, Vischer U, Woo J, Chapman I, Dunning T, Meneilly G, Rodriguez-Saldana J, Gutierrez Robledo LM, Cukierman-Yaffe T, Gadsby R, Schernthaner G, Lorig K. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. *J Am Med Dir Assoc* 2012; **13**: 497-502 [PMID: 22748719 DOI: 10.1016/j.jamda.2012.04.012]

39 IDF Global Guideline for Managing Older People with Type 2 Diabetes. [Accessed August 9 2014]. Available from: URL: http://www.idf.org/sites/default/files/IDF-Guideline-for-older-people-T2D.pdf

Baishideng®