Chapter 5

Age is an Important Risk Factor for Type 2 Diabetes Mellitus and Cardiovascular Diseases

Ketut Suastika, Pande Dwipayana,
Made Siswadi Semadi and R.A. Tuty Kuswardhani

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1. Introduction

A field study by World Health Organization (WHO), World Bank and Harvard University in 1990 found a changing pattern of diseases caused by unhealthy lifestyle changes that may eventually lead to metabolic syndrome, type 2 diabetes mellitus, coronary arterial diseases, depression, and traffic accidents (Kinsella and Phillips, 2005). The study also predicted that cerebrovascular diseases would become the most prevalent disease, whereas human HIV infection would sharply increase in the year 2020 (Kinsella and Phillips, 2005). The lifestyle-related and degenerative diseases are significant problems in the old aged population group.

The number of elderly population has increased worldwide, and recently it has been increasing sharply in the developing countries. The projection of the number of elderly population in Indonesia by the year 2010 is 23,992. The Indonesian Central Bureau for Statistics (*Badan Pusat Statistik*) has reported that Indonesia is the world's fourth in the number of elderly population after China, India, and USA (Komala *et al*., 2005). US Bureau of Census predicted that from 1990 to 2020, the Indonesian elderly population would increase to 41.4%. The predicted increased number of elderly was ascribed to the success of health promotion and improvement of social and economic status (Kinsella and Taeuber, 1993).

Metabolic disorders including type 2 diabetes mellitus (T2DM) and cardiovascular diseases are closely related with the aging process. Central obesity and insulin resistance as the initial preconditions and its consequences related to metabolic diseases and cardiovascular diseases are frequently found among the elderly. Decline in lean body mass and increase in body fat, particularly visceral adiposity that often accompanies aging, may contribute to the development of insulin resistance. As for the mechanism of T2DM, it is known that aging

induces a decrease of insulin sensitivity and alteration or insufficient compensation of beta cell functional mass in the face of increasing insulin resistance (Meneilly and Elliot, 1999). Related to beta cell functions, aging correlates with a decrease of beta cell proliferation capacity and enhances sensitivity to apoptosis (Maedler *et al*., 2006). It has recently been proposed that an age-associated decline in mitochondrial function contributes to insulin resistance in the elderly (Petersen *et al*., 2003). Other metabolic diseases are also frequently related with aging such as coronary arterial disease, malignancies, cognitive disorders, and vitamin D deficiency (Yaffe *et al*., 200; Lu *et al*., 2009).

2. Age and related risk factors for type 2 diabetes mellitus and cardiovascular diseases

2.1. Age, mitochondrial dysfunction and inflammation

Mitochondria, a membrane-enclosed organelle found in most eukaryotic cells, generate most of the cell's supply of adenosine triphosphate (ATP), are used as a source of chemical energy, and are involved in a range of other processes such as signaling, cellular differentiation, cell death, as well as the control of the cell cycle and cell growth. Mitochondria have been implicated in several human diseases, including mitochondrial disorders, aging process and cardiac dysfunction. Mitochondrial dysfunction is central to the theories of aging because age-related changes of mitochondria are likely to impair a host of cellular physiological functions in parallel and thus contribute to the development of all the common age-related diseases (Dai *et al*., 2012). Rising cellular oxidative stress due to any cause induces mtDNA and mitochondria damage and culminates in a mitochondria function crisis, cell death and aging. Otherwise, aging itself causes abnormal mitochondrial morphology and cell death or apoptosis (Seo *et al*., 2010). Judge *et al*. (2005) in their study on rats found that accumulation of oxidant-induced damage in interfibrillar mitochondria might be a major contributing factor to the age-related alterations in myocardial function. How old age can be a major risk factor for CVD via mitochondrial dysfunction has been completely reviewed by Dai *et al*. (2012).

Chronic inflammation is a characteristic feature of aging. A study by Sarkar et al. (2004) showed that human polynuleotide phosphrylase might play a significant role in producing pathological changes associated with aging by generating proinflammatory cytokines via reactive oxidative stress (reactive oxygen species(ROS) and NF-κB. The role of NF-κB in bridging the explanation of how aging is associated with inflammation and endothelial dysfunction is reviewed well by Csiszar *et al*. (2008). Another study has shown that depletion of cellular (GSH) during aging plays an important role in regulating the hepatic response to IL-1β (Rutkute *et al*., 2007). At rest, skeletal muscles of elderly people showed a lower number of macrophages, higher gene expression of several cytokines, and activation of stress signaling proteins, compared with skeletal muscles of young people (Peake et al., 2010). Human aging is associated with the development of insulin resistance, β-cell dysfunction and glucose intolerance. The level of suppression of the TNF-α production was observed and found to be significantly correlated with insulin action. Reduced

suppression of TNF-α production in the elderly may in part contribute to the decline in insulin sensitivity (Kirwan et al., 2001). Hyperglycemia in patients with prediabetes and diabetes is associated with inflammation (de Rekeneire *et al*., 2006).

2.2. Age and lipid metabolism

Aging and age are often associated with lipid metabolism disorders. Lipid metabolism disorders that are associated with aging process constitute the early stage in the emergence of a constellation of risk factors for metabolic disorders (Sawabe *et al*., 2009; Gobal and Metha, 2010). After the age of 20 years, low-density lipoprotein cholesterol (LDL-C) increases significantly in both men and women. LDL-C does not increase or is in a flat state between the age of 50-60 years (male) and 60-70 years (female) (Gobal and Mehta, 2010). On the other hand, high–density lipoprotein cholesterol (HDL-C) levels decrease during puberty to young adulthood (in males). Throughout their lives women have lower total cholesterol compared to men, but the levels will rise sharply after menopause and will be higher in the age >60 years as compared to men. Concentrations of triglyceride (TG) increase sharply in males, reaching a peak at the age 40-50 years and decline gradually thereafter. TG levels increase in women throughout their lives, especially in women taking estrogen replacement therapy (Gobal and Mehta, 2010).

With the increase of age the composition of body fat also increases, which especially accumulates in the abdomen triggering the incidence of central obesity. TG composition in the muscle and liver are higher in older age compared with younger age groups (Cree *et al*., 2004). Increased body fat composition is associated with reduced fat oxidation both at rest and in activity (Nagy *et al*., 1996). Aging (age) affects the release of fatty acids (FFA),from fat tissue (adipose), and the capacity of peripheral tissues such as muscles, to oxidize fat. These are some of the changes in lipid metabolism influenced by age and aging, which decreases lipolysis response and capacity of fat oxidation.

Lipolysis is modulated by various hormones such as catecholamines, glucagon, adrenocorticotropic hormone, growth hormone, prostaglandin, and thyroid hormone (Toth and Tchernof, 2000). Lipolysis response regulated by these hormones will decrease with aging. Decreased ability of catecholamines to stimulate lipolysis in the elderly is caused by decreased fat tissue response to adrenergic stimulation (Dillon *et al*., 1984). This response involves reduced role of protein kinase A, G-protein complex adenylil cyclase, or the stages in the cyclic AMP signaling cascade (Toth and Tchernof, 2000). Effects of insulin on plasma FFA was different between in the elderly compared with in younger subjects. Insulin infusions showed that plasma FFA, turnover and oxidation, and total lipid oxidation were higher significantly in the elderly than in the younger group (Bonadonna *et al*., 1994). Aging is also associated with decreased sensitivity to antilipolysis effects of insulin (Toth and Tchernof, 2000). Hence this will also increase the release of free fatty acids to the blood in the elderly.

Age is associated with decline in fat oxidation during activity, after meal and in resting condition (Robert *et al*., 1996). In principle, the capacity of metabolically active tissues such

as the muscles to oxidize fat represents a combination of the tissue mass and oxidative capacity of the tissue. Fat free mass decreases with age (Poehlman *et al*., 1992) and in resting condition fat oxidation tends to be influenced by the size of fat free mass itself. Changes in lipid metabolism in the aging process are associated with dysfunction of endothelial cells pseudocapillarization of the liver sinusoid. This change causes decreased endocytosis, increased leukocyte adhesion, decreased hepatic perfusion and will potentially reduce the passage of chylomicron remnants into hepatocytes (Denke and Grundy, 1990). After activity or after meal, fat oxidation rate is more influenced by the oxidative capacity of muscle tissue. Decreased muscle oxidative capacity with aging is associated with reduced activity of enzymes involved in oxidative metabolic processes (such as succinate dehydrogenase; citrate synthase; cytrochrome c oxidase) and β-oxidation of fatty acids (such as H-3-CoA dehydrogenase Hydroacyl) (Coggan *et al*., 1992; Rooyackers *et al*., 1996).

Changes in lipid metabolism due to aging will lead to increased accumulation of body fat, resulting in increased concentrations of free fatty acids in the blood/plasma, and disposal of non-oxidative or free fatty acids. Increased concentrations of free fatty acids in blood increases glucose production, and this will inhibit insulin-stimulated glucose uptake and decrease hepatic insulin extraction (Fanelli *et al*., 1993; Toth and Tchernof, 2000). The changes will be followed by insulin resistance and hyperinsulinemia. Disposal of non-oxidative free fatty acids into the liver will increase the formation of triglyceride-rich very low-density lipoprotein (VLDL) that plays a role in the formation of atherogenic dyslipidemia. Increased levels of TG and decrease HDL-C are features of atherogenic dyslipidemia in people with central obesity, hypertension and insulin resistance (Linblad et al, 2001). In relation to BMI, although older age correlates with lower BMI and higher fat mass, dramatically decreased insulin sensitivity and lack of physical activity are the most important risk factors for metabolic disorders in the elderly (Gobal and Metha, 2010; Linbald *et al*., 2001). Insulin resistance itself is associated with decreased glucose carrier protein in the muscle (Sawabe *et al*., 2009).

The incidence of heart attacks is higher in the elderly compared to middle age group with high cholesterol levels. Van der Meer *et al*. (2008) studied the association of myocardial TG content with diastolic function. They found that myocardial TG content was significantly associated with age ($r = 0.57$, $p < 0.05$) and TG was negatively related to left ventricular diastolic function ($r = 0.68$, $p < 0.05$). Multivariate analysis showed that myocardial TG content was an independent predictor ($p < 0.05$) for decreased diastolic function associated with age. Lower HDL cholesterol is an important risk factor for not only ischemic heart disease but also for cerebrovascular disease, especially in diabetic elderly individuals (Hayashi *et al*., 2009).

2.3. Age, insulin resistance and metabolic syndrome

Metabolic syndrome is a group of metabolic abnormalities of which central obesity and insulin resistance are believed to be the primary backgrounds. The diagnostic criteria for metabolic syndrome have been proposed by several organizations and associations, all of

which are based on five parameters i.e. central obesity, high blood pressure, high fasting blood glucose levels, high TG levels and low levels of HDL-C. The pathogenesis of how central obesity causes insulin resistance and metabolic syndrome has been explained in many publications. Decreased insulin sensitivity, reduced muscle mass, and increased body fat mass, especially visceral fat that accompanies aging contribute to insulin resistance in the elderly. Aging process is also associated with reduced compensatory beta cell mass function of the pancreas and to insulin resistance (Maneilly and Elliott, 1999) as well as with decreased mitochondrial function that contributes to insulin resistance (Petersen *et al*., 2003). A study by Gupta *et al*. (2000) showed that hepatic insulin resistant was related to body fat and its distribution, and hepatic insulin action could be preserved by caloric restriction in aging caloric restriction rat.

A study conducted in the metropolitan area of St. Louis on 100 women aged ≥ 65 years found higher fasting blood sugar levels in subjects with insulin resistance (94.1 ± 8.1 *vs.* 87.9 ± 8.2 mg/dl, p <0.05) (Banks *et al*., 2007). A study by Kuusisto *et al*. (2001) showed that the insulin resistance syndrome is a risk factor for coronary heart disease (CHD) in the elderly with a hazard ratio of 1.71. Insulin resistance as risk factor for cardiovascular disease (CVD) is associated with increase of acute phase protein response and inflammatory markers. The Rotterdam study that enrolled 574 non-diabetic elderly population showed that insulin correlated strongly and significantly with C-reactive protein (CRP), α-1-antichymotrypsin, interleukin (IL)-6 and soluble intercellular adhesion molecule-1, indicating that insulin resistance is an integral part of inflammation (Hak *et al*., 2001).A study by Suastika *et al*. (2011) on the population of Bali, Indonesia, has showed a tendency of increasing frequency of metabolic syndrome and its components with increasing age (Table 1). A study on the elderly by Zambon *et al*. (2009) found that metabolic syndrome was associated with increased mortality by various causes (HR 1:41) and mortality from CVD (HR 1.60). The association of metabolic syndrome and increased frequency of carotid plaque and thickening of the carotid artery intima media in elderly subjects (aged 65-85 years) was noted in a study by Empana *et al*. (2007). Subjects with metabolic syndrome have two-fold higher levels of oxidized LDL-C than those without Metabolic syndrome, and they are associated with increased risk of myocardial infarction with relative risk of 2.25 (Holvoet *et al*., 2004). Metabolic syndrome in the elderly was associated with two-times increase of CRP levels (3.1 *vs*. 1.5 mg/l), compared with the elderly without metabolic syndrome (Hassinen, 2006).

Decreased physical activity/less exercise in the elderly has also contributed to the occurrence of obesity and metabolic syndrome. A study by Hahn *et al*. (2009) on subjects aged 55-74 years found that regular exercise at least ≤1 hour per week reduced the risk of metabolic syndrome. Sports activities >2 hours per week would be effective in lowering the risk of metabolic syndrome.

3. Age and type 2 diabetes mellitus

Similar to metabolic syndrome, the prevalence of impaired fasting glycemia (IFG) and T2DM increase with rising age. In the United States, the estimated percentage of people

aged 20 years or older having diagnosed or undiagnosed diabetes in 2005-2008 was increasing with age. In the age group of 20-44 years, it was estimated about 3.7% people had diabetes; while in the age group 45-64 years the number increased to 13.7%; and the highest percentage of 26.9% was found in the age group of ≥ 65 years (Centers for Disease Control and Prevention, 2011). Similar feature was also observed n England, where the prevalence of diabetes was increasing with age. The peak prevalence of diabetes can be found in the age group of 65-74 years with 15.7% in men and 10.4% in women (Shelton, 2006). The study by Suastika *et al*. (2011) on Bali population showed that the prevalences of IFG and T2DM were higher in the elderly than in the younger age group, i.e. nearly two-fold and more than two fold, respectively (Figure 2). There was a tendency of increasing frequency of IFG and T2DM with increasing age (Table 2). Data from rural Taiwan showed that prevalence of DM was 16.9% and that of IFG was 25.5% among elderly Chinese in 2000. During a 5 year follow up, cumulative prevalences of DM and IFG were 23.7% and 27.9%, respectively. The 5-years cumulative incidence of newly onset diabetes was 6.8%. Hypertension, overt proteinuria, IFG and high total cholesterol were independent risk factors for new onset diabetes (Peng *et al*., 2006).

Metabolic syndrome and its components	~19 (%)	20-29 (%)	30-39 (%)	40-49 (%)	50-59 (%)	60-69 (%)	≥70 (%)
Metabolic syndrome	5.5	4.8	15.9	17.6	29.6	26.0	17.3
Increased waist circumference	12.5	24.6	37.9	40.1	43.6	29.7	13.8
Elevated triglyceride	1.7	10.3	24.6	26.1	31.3	25.9	18.3
Reduced HDL-cholesterol	25.9	31.3	34.2	27.6	30.2	33.5	31.4
Elevated blood pressure	12.5	15.1	19.2	31.5	45.8	55.1	60.0
Elevated fasting blood glucose	6.9	9.5	12.9	17.3	27.4	34.9	29.9

Suastika et al. J Clin Gerontol Geriatrics 2011; 2: 47-52.

Table 1. Frequency of metabolic syndrome and its components, by age (years)

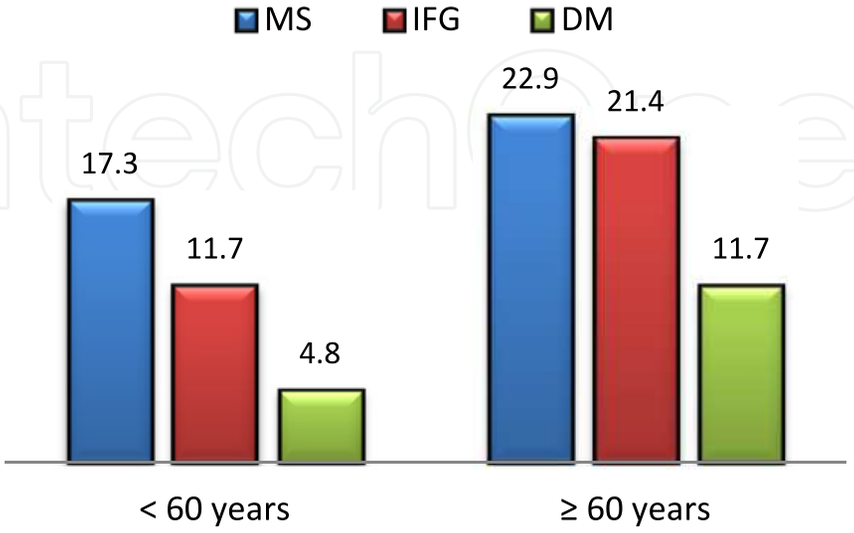

Figure 1. Frequency of metabolic syndrome (MS), impaired fasting glycemia (IFG), and diabetes mellitus (DM) in the younger-aged and elderly. Suastika et al. J Clin Gerontol Geriatrics 2011; 2: 47-52.

The prevalence of glucose intolerance (pre-diabetes and T2DM) increases with advancing age. Some factors involve in the pathophysiology of glucose intolerance in the elderly. The main factors are that aging induces decrease insulin sensitivity and alteration or insufficient compensation of beta cell functional in the face of increasing insulin resistance (Chang and Halter, 2003). Decrease in beta cell proliferation capacity and enhanced sensitivity to apoptosis are the states related with aging (Maedler *et al*., 2006). A study by Szoke *et al*. (2008) showed that the first and second phase of insulin secretion normally decreases at the rate of approximately 0.7% per year with aging, this decrease in β cell function is accelerated about two-fold in people with impaired glucose tolerance. But aging per se has no effect on insulin sensitivity independent of change in body composition. Decline in lean body mass and the increase in body fat particularly visceral adipocytes ("central obesity") that accompanies aging may contribute to insulin resistance. It has recently been proposed that an age-associated decline in mitochondrial function contributes to insulin resistance in elderly. Mitochondrial oxidative and phosphorylation function was reduced about 40% in association with increased intramyocellular and intrahepatocellular lipid content and decreased insulin-stimulated glucose uptake (Petersen *et al*., 2003). The pathophysiological basis of sarcopenia (loss of muscle mass with age) has a relationship with oxidative stress, reduced neuronal stimulation, subclinical inflammatory and insulin resistant state. Those conditions contribute to the development of glucose intolerance and type 2 diabetes (Khamseh *et al*., 2011).

Minamino *et al.* (2009) in their study on mice proposed a model in which aging and inflammation was initiated in adipose tissue and subsequently induced insulin resistance in adipose tissue, liver and muscle. They also proposed that adipose tissue p53 tumor suppressor mediated the lipid abnormalities and cardiovascular morbidity associated with obesity. The study found that excessive calorie intake caused accumulation of oxidative stress in the adipose tissue of mice with type 2 diabetes–like disease and promoted senescence-like changes, such as increased activity of senescence-associated β-galactosidase, increased expression of p53 and increased production of proinflammatory cytokines. Inhibition of p53 activity in adipose tissue decreased the expression of proinflammatory cytokines and improved insulin resistance. Conversely, up-regulation of p53 in adipose tissue caused an inflammatory response that led to insulin resistance.

Classification	~19 (N=59)	20-29 (N=201)	30-39 (N=454)	40-49 (N=490)	50-59 (N=304)	60-69 (N=199)	≥70 (N=111)
Normoglycemia	93.1	90.5	87.1	82.7	72.6	65.1	70.1
Impaired fasting glycemia	6.9	7.0	10.9	11.7	16.9	23.4	17.8
Diabetes mellitus	0	2.5	2.0	5.6	10.5	11.5	12.1

Suastika et al. J Clin Gerontol Geriatrics 2011; 2: 47-52.

Table 2. Frequency of glycaemic status (), by age (years)

4. Age and cardiovascular diseases

Cardiovascular disease remains to be the most important cause of death in all countries over the world. Although certain reports from some developed countries indicate the incidence tends to decrease, from many countries there are reports mentioning that its incidence tends to increase. Cardiovascular disease is a complex disease; too many risk factors are involved in its pathogenesis. In general, risk factors for CVD can be divided into two main groups, namely traditional and non-traditional risk factors. Traditional risk factors include age (older than 40 years for men, 45 years for women), male sex, family history of coronary heart disease, smoking, hypertension, diabetes, central obesity, unhealthy cholesterol levels (high total cholesterol, low high-density lipoprotein [HDL] cholesterol, high low-density lipoprotein [LDL] cholesterol, high triglycerides), and low physical activity (Fonseca *et al*., 2004; Torpy *et al*., 2009). In addition, some non-traditional risk factors for CVD are reported elsewhere (Fonseca *et al*., 2004; Vasan, 2006; Helfland *et al*., 2009).

Several reviews have stressed that age is the strongest risk factor for CVD (Ref). Age itself may be an independent risk factor or may have other risk factors related to aging or exposure to risk factors during their lifetime. In the United States, CVD was the leading cause of death for persons 65 years of age and over in 2007, which accounted for 28% of deaths in this age group (National Center for Health Statistics, 2011). In Asian population, age is also one of the most important determinants of CVD. The studies by Suastika *et al.* in a remote area of Ceningan Island found that coronary heart disease (CHD) prevalence was relatively high (11.5%), and older age (male ≥45 years and female ≥55 years) had higher risk for CHD than younger age group (OR, 27.0). By logistic regression analysis of all variables of the risk factors, age (β=3.937) consistently appeared to be the risk factor for CHD (Suastika *et al*., 2012a). Age in the group with CHD (old myocardial infarction and myocardial ischemia) was significantly higher than those without CHD (65.0 *vs.* 58.5 *vs*. 40.5 years) (Suastika *et al*., 2012b).

Several changes in cardiovascular system related with aging include changes in vascular function (increase wall thickening and arterial stiffening, endothelial dysfunction) and cardiac function (heart rate and cardiac output, left ventricular wall function and myocardial contraction). The stiffness of arterial walls increase with age. This increase includes luminal enlargement with wall thickening and a reduction of elastic properties at the level of large elastic arteries. Long standing arterial pulsation in the central artery has a direct effect on the structural matrix proteins, collagen and elastin in the arterial wall, disrupting muscular attachments and causing elastin fibers to fatigue and fracture. Increased vascular calcification and endothelial dysfunction is also characteristic of arterial aging. These changes lead to increased pulse wave velocity, especially along central elastic arteries, and increase in systolic blood pressure and pulse pressure (Lee and Oh, 2010). Aging cardiovascular tissues are exemplified by pathological alterations including hypertrophy, altered left ventricular (LV) diastolic function, and diminished LV systolic reverse capacity, increased arterial stiffness, and impaired endothelial function. Study by Cheng *et al*. (2009) revealed that age was associated with a phenotype of LV remodeling

marked by increased mass-to-volume ratio and accompanied by systolic as well as diastolic myocardial dysfunction that is not reflected by preserved ejection fraction. This pattern of ventricular remodeling confers significant cardiovascular risk, particularly when present earlier in life.

Peripheral artery disease (PAD), a marker of systemic atherosclerosis, is frequently related with age. It mostly starts at 40 and increases after the age 70 years. PAD is the independent risk factor for mortality caused by CVD (Norman *et al.*, 2004). A study by Kuswardhani and Suastika (2010) on elderly patients who visited the Geriatric Outpatient Clinic, Sanglah Hospital showed that diabetic patients with PAD had higher age (70.7 *vs*. 65 years, p<0.001) and higher homocystein levels (13.4 *vs*. 11.5 mmol/L, p = 0.023), compared with those without PAD. High age (70-80 years) had 7.4 times risk than those with lower age (60-69 years) and high homocystein levels (≥ 11 mmol/L) had 2.5 times risk than those with lower homocystein levels, to develop PAD. By multivariate analysis (logistic regression), it was found that only age played a role in PAD event.

How the age/aging relates to T2DM and CVD based on above review is summarised in Figure 2.

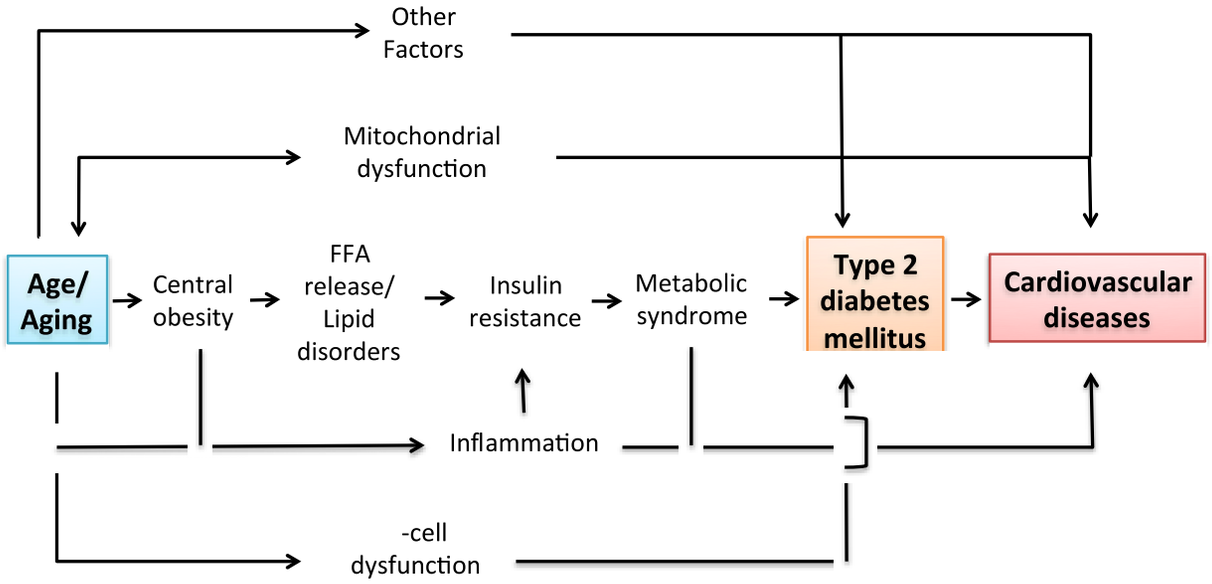

Figure 2. Summary of the relationship between age/aging and type 2 diabetes mellitus and cardiovascular diseases. .

5. Conclusion

The number of elderly population has increased worldwide, and recently it has been increasing sharply in the developing countries. Prolong survival in the elderly creates an impact on the appearance of metabolic diseases and CVD. Increase in the prevalence of metabolic diseases (such as T2DM and CVD) in old age may be related directly with age or aging process itself or indirectly through several other age-related risk factors of T2DM and CVD such as central obesity, mitochondrial dysfunction, FFA and lipid metabolisms

disorders, inflammation, β-cell dysfunction, insulin resistance, metabolic syndrome, and other factors which are not discussed in this review.

Author details

Ketut Suastika, Pande Dwipayana and Made Siswadi Semadi
Division of Endocrinology and Metabolism, Internal Medicine, Faculty of Medicine, Udayana University, Sanglah Hospital, Denpasar, Indonesia

RA Tuty Kuswardhani
Division of Geriatrics; Department of Internal Medicine, Faculty of Medicine, Udayana University, Sanglah Hospital, Denpasar, Indonesia

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