

Is shortening of telomeres the missing link between aging and the Type 2 Diabetes epidemic?

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Commentary on: Doreen Kuhlow et al. *Telomerase deficiency impairs glucose metabolism and insulin secretion. Aging. 2010; 2: this issue*
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The world is facing an impending epidemic of diabetes [1]. Diabetes occurs in two forms – Type 1 and Type 2. These are separate entities, although they share an elevation of fasting plasma glucose (≥ 7.0 mM or 126 mg/dl) as the only required diagnostic criterion. The diabetes epidemic can be attributed to Type 2 Diabetes. Historically, Type 2 Diabetes has been a disease of the aged population. Recently, a drift in the incidence is observed, with younger individuals developing Type 2 Diabetes.

Concurrently, life expectancy in the world is increasing [2, 3]. This implies that health care will have to deal with an increased prevalence of diseases afflicting people of higher age. Aging is a well-established risk factor for Type 2 Diabetes. Pathogenetic processes linked to aging are thought to play a major role in development of the disease. Type 2 Diabetes arises as impaired insulin sensitivity of the peripheral target tissues of insulin, i.e., skeletal muscle, liver and adipose tissue, combines with insufficient insulin secretion. It is widely embraced that both insulin secretion and insulin sensitivity are reduced in the aged. Thus, in the insulin-resistant individual, insulin secretion, in the genetically predisposed, can not overcome impaired action of insulin. This results in elevated plasma glucose, the hallmark of diabetes.

In the recent years, global and unbiased analyses of genetic variability in large cohorts of patients with Type 2 Diabetes and individuals with metabolic traits have changed how we perceive the pathogenesis of Type 2 Diabetes [4]. These studies are known as genome-wide association studies (GWAS) and have now generated in excess of 50 genes, which are firmly linked to Type 2 Diabetes or relevant metabolic traits [5]. This list of

genes is continuously expanded. Perhaps the greatest insight from these studies is that the vast majority of genes associated with Type 2 Diabetes seem to be relevant for the function of the insulin-secreting β -cell [6]. β -cells are located in the islets of Langerhans, the endocrine portion of the pancreas. They sense plasma glucose levels and secrete insulin. The hormone controls whole body metabolism by stimulating glucose uptake in skeletal muscle and adipose tissue, while inhibiting glucose production from the liver. In fact, some of the associated genes identified by the GWAS could be envisioned to play a role in control of the β -cell. This would, at least in part, determine the insulin-secretory capacity in a given individual. The genes include *CDKN2A/B* and *CDKAL1*, which are involved in cell cycle regulation, *IGF2BP2*, *HHEX/IDE* and, *CDC123/CAMK1D*, which are implicated in growth as well as a host of transcription factors such as *TCF7L2*, *NOTCH2*, and *HNF1B (TCF2)*, which are thought to control β -cell development. While the GWAS have lent support to the critical role of β -cell mass in the development of Type 2 Diabetes, its importance has been hotly debated over the years. Currently, a view is favored where insufficient adaptation of β -cell mass to insulin resistance plays a pathogenetic role. This is supported by extensive analyses of autopsy-derived pancreatic specimens from patients with Type 2 Diabetes [7, 8].

In this issue of Aging, Kuhlow and colleagues report data, which fill in a gap in our understanding of the pathogenesis of Type 2 Diabetes, aging and control of β -cell mass [9]. They describe studies in which telomerase deficiency in mice results in perturbed glucose metabolism due to an impairment of insulin secretion. The enzyme telomerase is responsible for the extension of chromosome ends with repeated DNA

sequences. These six-nucleotide repeats constitute the telomere and allow faithful replication of DNA at the chromosomal ends. However, when telomeres are shortened, which is known to occur with age, DNA replication is thought to slow down, ultimately leading to senescence of cells. For this reason, telomeres have been implicated in research on senescence and aging. Also in diabetes research, telomere shortening has been linked with Type 2 Diabetes [10]. Some work has addressed a possible role of telomerase in β -cell regeneration [11]. However, for the most part, these links have been found when analyzing telomere length in circulating leukocytes in patient cohorts. A shortcoming of such studies is that we are not provided with any information about telomere length in the actual cells and tissues involved in metabolic homeostasis. Kuhlow and colleagues bring a new perspective to the research field, since they examined telomere length in the relevant tissue, the pancreatic islets.

The gene for the reverse-transcriptase part of telomerase, *Terc*, was targeted (*Terc*^{-/-}) in mice [9]. The *Terc*^{-/-} mice were normoglycemic and exhibited unaltered insulin levels in the basal state. However, upon a challenge with glucose, the sugar was eliminated at a slower rate in the face of less insulin being released. Insulin sensitivity was seemingly unaffected, as reflected by in vivo insulin tolerance. This points to the β -cell as the culprit, and was reinforced by the finding of reduced average telomere length in islets.

The authors proceeded to unravel whether a reduction in β -cell mass or function accounted for the deficiency of insulin secretion. They found that several parameters reflecting β -cell mass were perturbed in the *Terc*^{-/-} mice.

Although the studies by Kuhlow and colleagues have shed new light on the possible role of telomeres in the pathogenesis of Type 2 Diabetes, some questions remain. At this point, the data indicate that β -cell mass is primarily affected by reduced telomerase length. It would be interesting to know if also the function of β -cells was affected. In human Type 2 Diabetes, a deficiency of β -cell function must likely add to a reduced β -cell mass to create an impairment of insulin secretion [8]. Moreover, islets are composed of several cell types in addition to β -cells, particularly the glucagon-secreting β -cell. It would be interesting to know whether telomere shortening affects this important cell type. Also, there are likely to be many molecular events linking shortening of telomeres with the impaired replication that was observed by Kuhlow and colleagues. This deserves further investigation. Finally, more information about telomere length in human islets and about genetic variation in genes relevant to control of telomere length in subjects with Type 2 Diabetes should be acquired. Nevertheless, the study by Kuhlow and colleagues represents an important step towards better understanding of the link between aging and Type 2 Diabetes.

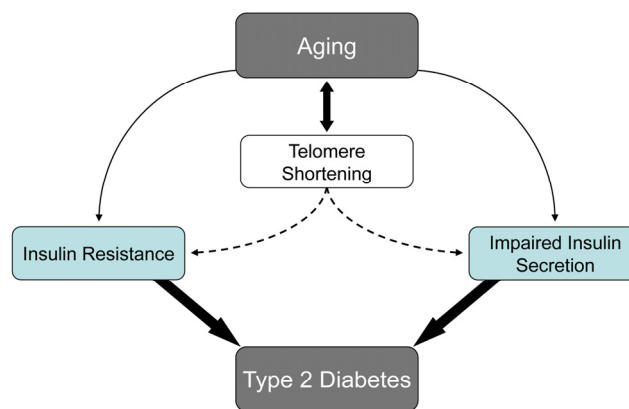


Figure 1. Aging is a well-established risk factor for Type 2 Diabetes. Both insulin secretion and insulin sensitivity, the major pathogenetic processes in Type 2 Diabetes, become impaired with increasing age. Telomere shortening occurs with aging. Studies suggest that this process may be linked with impairments of both insulin secretion and insulin sensitivity.

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