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FOR DEBATE

Chromosomal telomere attrition as a mechanism for the increased risk of epithelial cancers and senescent phenotypes in type 2 diabetes

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Abstract Telomeres are the repeat DNA sequences at the end of chromosomes necessary for successful DNA replication and chromosomal integrity. Telomeres shorten at cell division at a rate determined by oxidative DNA damage, and cells are triggered into replicative senescence once telomeres shorten to a critical length. Telomere-related chromosomal maintenance also has a role in carcinogenesis. Type 2 diabetes is characterised by increased oxidative stress, increased oxidative DNA damage, senescent retinal and renal phenotypes, and an increased risk of epithelial malignancy. We suggest that increased oxidative DNA damage and telomere attrition in type 2 diabetes leads to: (1) carcinogenic telomere-dependent chromosomal non-reciprocal translocations, genomic instability, and the development of epithelial cancers; (2) senescent retinal and renal phenotypes (expressed as diabetic retinopathy and nephropathy); and (3) senescent vascular endothelial, monocyte-macrophage and vascular smooth muscle cells (expressed as endothelial dysfunction and accelerated atherogenesis). An adverse intrauterine environment leads to increased feto-placental oxidative stress and feto-placental oxidative DNA damage. We also suggest that intrauterine oxidative DNA damage and telomere shortening is another point at which increased oxidative stress could contribute to a pre-programmed increased risk of senescent phenotypes in adult offspring, characterised by type 2 diabetes and epithelial malignancy. These suggestions can be used to understand early glucose intolerance in the young children of type 1 diabetes pregnancies, poor cancer outcomes in type 2 diabetes, beta cell fatigue in type 2 diabetes and the absence of increased epithelial cancer risk in type 1 diabetes.

Keywords Atherosclerosis · Cancer · DNA · Oxidative stress · Pre-programming · Senescence · Telomere · Type 2 diabetes

Abbreviations

IUGR	intrauterine growth retardation
NRT	non-reciprocal translocation
RPE	retinal pigment epithelial cells

Introduction and background

Eukaryotic chromosomes are capped with telomeres, tandem repeats of the DNA sequence TTAGGG extending over 6 to 15 kb, which are necessary for successful DNA replication and chromosomal integrity [1]. Telomeres in somatic human cells shorten at cell division, and once shortened to a critical length cells are triggered into replicative senescence [2], an irreversible cell cycle block in G0/G1. Cells trapped in replicative senescence function differently, and some senescent cell types are more likely to undergo apoptosis if exposed to continued oxidative damage [3–5]. Rates of telomere shortening at cell division are highly dependent on oxidatively induced strand breaks in telomeric DNA, on cellular oxidant balance, and on the protection offered by the reverse transcriptase telomerase

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and other telomere-maintenance proteins [6]. The GGG sequence in telomeres is particularly prone to DNA damage, and telomeric DNA is more prone to oxidatively induced single-strand breaks than non-telomeric DNA [7]. Recently, we have shown both that type 2 diabetes is characterised by increased susceptibility to oxidative DNA damage and that telomere attrition is directly related to levels of oxidative DNA damage in monocytes [8, 9]. Epithelial cells with substantial telomeric disruption are more prone to develop chromosomal disorganisation and carcinogenic chromosomal non-reciprocal translocations [NRTs] in epithelial cells [10, 11]. Recent surprising observations have confirmed an increased risk of many cancers in type 2 diabetes [12], in addition to the established renal, retinal and vascular complications, and the mechanisms underlying this association remain unclear. A substantial and separate literature also supports an association between an adverse intrauterine environment and the later development in offspring of an increased risk of atherogenesis, hypertension and type 2 diabetes [13–15]. Feto-placental telomere attrition has attracted interest as a hypothetical bridge between the intrauterine environment and these conditions, although much of this interest is derived from in vitro models rather than clinical or epidemiological studies [3–5].

For debate

We suggest that increased oxidative DNA damage in type 2 diabetes leads to telomeric DNA damage in many cell types, to accelerated telomere shortening at cell division, and to senescent phenotypes in multiple cell types. We suggest that this leads to: (1) the development of chromosomal NRTs, genomic instability and an increased risk of epithelial malignancies; (2) accelerated endothelial and vascular cell senescence (expressed as endothelial dysfunction and atherogenesis); (3) progressive beta cell senescence (expressed as beta cell failure); and (4) senescent renal and retinal phenotypes (expressed as diabetic nephropathy and retinopathy). Separately, as an adverse intrauterine environment leads to increased feto-placental oxidative stress and DNA damage, we suggest that this leads to telomere attrition in multiple fetal cell types, pre-programming offspring towards a senescent adult phenotype of endothelial dysfunction, atherogenesis, pancreatic beta cell senescence and type 2 diabetes. Pre-programmed telomere shortening in epithelial cells would predispose this phenotype towards an increased risk of epithelial-derived malignancies. These testable suggestions could also account for some of the less understood senescent characteristics associated with type 2 diabetes and are compatible with much existing data.

Adverse intrauterine environment, oxidative DNA damage and telomere attrition

Increased oxidative stress and oxidative damage to feto-placental DNA and fetal vascular endothelium mediate drug-, ethanol- and diabetes-induced embryopathies in animal models [16]. An adverse intrauterine environment and intrauterine growth retardation [IUGR] are also associated with increased maternal, fetal and placental oxidative DNA damage [17]. Telomere length in somatic cells originates from telomere-length programming in the germ line [18] and telomere maintenance by the reverse transcriptase telomerase is downregulated in the later stages of fetal development, in some fetal tissues, and in placental tissues in IUGR [19, 20]. Increased feto-placental oxidative DNA damage in an adverse intrauterine environment could pre-programme multiple fetal cell types towards telomere attrition and replicative senescence, as it is biologically highly plausible that increased oxidative stress and DNA damage in the feto-placental unit translates into fetal telomere damage and shortening [1, 2, 7]. If this were the case, one would expect the newborn and infant offspring born from an adverse intrauterine environment to demonstrate (a) senescent phenotype(s). Many groups have in fact made the striking observation that the very young children of mothers with pre-conception type 1 diabetes (an archetype for a severely adverse intrauterine environment) have a prematurely aged phenotype characterised by glucose intolerance, endothelial dysfunction, early markers of atherogenic risk and psychomotor deficits [21].

Telomere attrition and increased malignancy risk in type 2 diabetes

The consistently increased risk of many epithelial cancers, particularly gastro-intestinal cancers, in type 2 diabetes has been reviewed recently [12]. Although confounding by obesity and dietary factors is possible, this association remains unexplained. Telomeric integrity is necessary for genomic stability, and telomere-length abnormalities in epithelial cells are an extremely early observation in the development of many epithelial-derived tumours [22], although there is a lack of prospective epidemiological evidence linking antecedent telomere attrition with increased cancer risk [23]. However, the association between epithelial telomere-length abnormalities and the earliest stages of epithelial cancer development, including the transition from adenoma to carcinoma in colorectal epithelial cells, has often been observed [22, 24]. Progressive telomere attrition and replicative senescence in epithelial cells could be seen as a tumour-suppressor mechanism, as cells triggered into senescence are unresponsive to growth

factors, and have no mitotic potential [10, 11, 25]. However, there is now significant evidence that telomere shortening during cell proliferation promotes genomic changes that predispose towards the development of epithelial cancers. In particular, telomere shortening in animal and human models promotes epithelial cell tumours through the chromosomal fusion-bridge breaking NRTs of chromosomal material and genomic instability which characterise carcinogenesis [10, 11, 25–27], and particularly epithelial carcinogenesis [10]. Data have appeared supporting a linkage between the intrauterine environment, increased fetal DNA damage and later cancer risk in animal models [28] and in humans [29, 30], although the data in humans are conflicting and confounded by obesity [30]. We suggest that the development of type 2 diabetes with increasing oxidative stress leads to oxidative DNA damage [9, 10] in mitotically active epithelial cells, leading to telomere attrition and an increased risk of epithelial cell tumours through fusion-bridge breaking, NRTs and genomic instability [10, 11, 25–27]. The poorer outcomes in type 2 diabetes patients for recurrence-free survival rates and median survival [12] could also be related to this hypothesis, with type 2 diabetes driving a progressive repopulation of carcinogenic genomically unstable epithelial cells [10, 11, 25–27]. In this context, it is important to note that evidence of a substantially increased risk of epithelial cancers in type 1 diabetes is lacking [12], and that we and others have shown that increased DNA oxidative susceptibility is not a feature of type 1 diabetes [31], perhaps because of more effective DNA repair mechanisms in younger type 1 patients [32]. We also suggest, although the epidemiological evidence is lacking, that an adverse intrauterine environment could be one variable that predisposes towards both type 2 diabetes and an increased risk of epithelial malignancies through feto-placental pre-programming of epithelial and other cell types mediated through telomere attrition.

It should be stressed that there are other proposed mechanisms for the association between some epithelial cancers and type 2 diabetes. Firstly, one potential confounding variable is exposure to an antecedent diet or lifestyle that contributes to an increased risk of both type 2 diabetes and cancer [33, 34]. Secondly, obesity may be an independent contributor to both conditions [34]. Another dominant hypothesis, for colorectal malignancy in particular, is that hyperinsulinaemia and increased insulin-like growth factors in type 2 diabetes or insulin-resistant populations have a direct action on colonic mucosal cell proliferation, differentiation and carcinogenesis. This has been well reviewed recently, although causality is not established [33, 34]. These mechanisms and the present suggestions are not mutually exclusive, and there may in fact be some overlap. Recently, it has been shown that increasing insulin resistance associated with weight gain [35], or peripheral insulin resistance [36], are significantly inversely associated with leucocyte telomere length, and that increased oxidative stress and telomere damage may be one contributor to these observations [35, 36].

Telomeres, replicative senescence and atherogenesis in type 2 diabetes

Endothelial dysfunction may precede the development of type 2 diabetes, peripheral insulin resistance and atherogenesis, and while endothelial dysfunction may antedate and contribute to these diseases it is unclear why it should develop initially [37, 38]. The phenotype of dysfunctioning vascular endothelial cells in these conditions is very similar to the senescent endothelial phenotype described in vitro [39], and the role of telomere attrition as a pre-programming mechanism towards endothelial senescence and dysfunction has been reviewed [4–6]. We suggest that increased oxidative DNA and telomere damage in type 2 diabetes, promotes a characteristic endothelial senescence and dysfunction, monocyte-macrophage and vascular smooth cell senescence and dysfunction, and promotes atherogenesis. We also suggest that an adverse intrauterine environment and feto-placental DNA damage and telomere attrition could be a contributor towards an adult phenotype of endothelial dysfunction associated with type 2 diabetes and beta cell failure in some subjects.

Telomere attrition and beta cell replicative senescence

Progressive pancreatic beta cell senescence and failure are early features of type 2 diabetes, and hyperglycaemia leads to progressive loss of beta cell mass with increased rates of beta cell senescence and apoptosis, in part mediated through oxidative stress [40]. Beta cell telomere shortening predicts the risk of beta cell growth arrest and senescence in human adult islet cell cultures, where telomere erosion appears to occur at a faster rate than in other cell lines [41]. In animal models, IUGR predisposes to fetal mitochondrial dysfunction, increased reactive oxygen species (ROS) generation, mitochondrial DNA damage, and progressive beta cell failure in the adult offspring [42]. Increased mitochondrial ROS generation should also translate to beta cell chromosomal DNA and telomere damage in IUGR models. Oxidative DNA damage and upregulated DNA repair mechanisms are recognised in the beta cell in type 2 diabetes [43], and there is an inverse relationship between beta cell volume density and levels of DNA oxidation products in human type 2 diabetes [44]. We suggest that type 2 diabetes leads to accelerated oxidative damage to

beta cell telomeric DNA, with progressive beta cell senescence and failure. This suggestion is compatible with the natural history of beta cell failure in type 2 diabetes, and with the unexplained failure of beta cell mass to increase in response to progressive hyperglycaemia [40]. We also suggest that one contributor to later beta cell senescence and failure in some subjects could be antecedent fetal pre-programming due to increased feto-placental oxidative stress and telomeric DNA damage in IUGR pregnancies.

Telomeres, replicative senescence and diabetic nephropathy

An adverse intrauterine environment leads to reduced renal glomerular numbers in offspring of animal models and humans, and to an increased risk of glomerular hyperfiltration, proteinuria and hypertension [45]. Accelerated renal cortical cell senescence and telomere shortening have also been described in humans and in animal models of renal disease in relation to an adverse fetal environment by Hales and colleagues [46]. The phenotype of diabetic nephropathy in type 2 diabetes is characterised by a high prevalence of non-progressive low-level proteinuria ('microalbuminuria') close to diagnosis of type 2 diabetes and associated for unknown reasons with endothelial dysfunction, exceptionally high rates of associated cardiovascular disease and little evidence of a significant genetic contribution [47]. We suggest that increased renal oxidative DNA damage in type 2 diabetes, a predictor of diabetic nephropathy [48], is associated with telomere damage and attrition, which allows early expression of a renal phenotype of progressive glomerular cell senescence and proteinuria associated with accelerated endothelial and vascular cell senescence and atherogenesis. We also suggest that subjects with an antecedent history of IUGR, programmed towards reduced glomerular numbers [45, 46], would be particularly prone to developing a senescent renal cortical phenotype if they developed type 2 diabetes. The observation of more effective DNA repair mechanisms in type 1 diabetes, with little evidence of increased oxidative DNA susceptibility compared with type 2 diabetes [31, 32], could account for the earlier onset of a senescent renal phenotype and proteinuria in type 2 diabetes than in type 1 diabetes.

Telomeres, replicative senescence and diabetic retinopathy

Endothelial dysfunction (and presumably retinal vascular endothelial dysfunction) is closely and directly related to the risk of diabetic retinopathy [49]. Retinal pigment epithelial (RPE) cells have a central role in maintaining retinal matrix and macular structure and function [50–52]. Damaged RPE cells demonstrate increased telomere shortening and senescence [53, 54]. We suggest that development of type 2 diabetes promotes oxidative DNA damage and telomere-associated senescence in retinal endothelial and RPE cells, and the senescent phenotype of diabetic retinopathy. This suggestion would fit with the particular risk of RPE-dependent maculopathy in type 2 diabetes, and the independent association between retinopathy and adverse cardiovascular outcomes [55]. The observation of more effective DNA repair mechanisms in type 1 diabetes, with little evidence of increased oxidative DNA susceptibility compared with type 2 diabetes [31, 32] could account for the earlier onset of a senescent retinal phenotype in type 2 diabetes compared with type 1 diabetes.

Existing data in type 2 diabetes and insulin resistance

We have shown an inverse association between oxidative DNA damage and telomere length in circulating mononuclear cells in type 2 diabetes (r=−0.55; p=0.018), and increased oxidative DNA damage in type 2 diabetes [8, 9], both of which support the necessary central argument for the link between oxidative DNA damage and telomere attrition. Aviv et al. [36] recently described a significant inverse relationship (r=−0.149; p=0.001) between leucocyte telomere length (adjusted for age and smoking) and measures of peripheral insulin resistance in 833 premenopausal women, although this relationship was absent in 683 postmenopausal women [36]. Similar inverse relationships between leucocyte telomere length and increasing peripheral insulin resistance (r=−0.47; p<0.01) were described in 70 subjects in the Bogalusa Heart study cohort [35], and in South Asian populations (r=−0.4; p=0.01; n=40) without type 2 diabetes [56]. The latter group also described lower leucocyte telomere length (p=0.00001) in a South Asian type 2 diabetes group compared with controls [56]. Increased oxidative stress was suggested as one possible contributor to leucocyte telomere shortening in these groups [35, 36, 56], and this would be compatible with the present hypothesis.

Implications

These testable suggestions are to some degree independent of existing models for associations between cancer and type 2 diabetes, between oxidative stress and the complications of type 2 diabetes, and between the intrauterine environment and some adult phenotypes. The difficulties in testing these suggestions will be in distinguishing between pre-programming models of telomere shortening and downstream

attritional models where diabetes or atherosclerosis influence telomere attrition. In particular, the potential confounding effects of obesity on these associations should be emphasised. To distinguish between these models we need (1) large, long-term, prospective epidemiological studies on telomere length and maintenance from infancy onwards in normal populations, linked to disease registries (cancer and diabetes) and to recorded birthweight; and (2) retrospective analyses of telomere length in stored telomere DNA in large disease registries (cancer, diabetes and diabetes complications) linked to birthweight data. In the short-term, we predict ten testable consequences of these suggestions:

(1) Telomere length in cord blood leucocyte and circulating vascular endothelial cells will be significantly lower at delivery in small-for-gestational-age offspring who have experienced an adverse intrauterine environment, compared with controls matched for gestational age.
(2) Telomere length in peripheral blood leucocyte, skin fibroblasts and epithelial cells in healthy young children and adolescents will be independently and inversely related to the later risk of developing both type 2 diabetes and epithelial cell malignancy, and directly to birthweight.
(3) Telomere length in bone marrow-derived circulating progenitor vascular endothelial cells, repopulating the vascular endothelium, will be independently and inversely related to biomarkers of endothelial dysfunction in adults.
(4) Telomere length in peripheral blood leucocyte, skin fibroblast and epithelial cells in existing elderly population cohorts with recorded birthweight but without type 2 diabetes or vascular disease will be directly and independently related to birthweight.
(5) Cross-sectional studies will demonstrate shorter telomere length in leucocytes, skin fibroblasts and epithelial cells from non-diabetic subjects in the upper quartile of the peripheral insulin-resistance range, independently of confounding by inflammatory markers.
(6) Low birthweight will be an independent predictor of increased risk of diabetic nephropathy and retinopathy, the early appearance of these conditions, and of early beta cell failure in type 2 diabetes.
(7) Telomere length in the colonic epithelial cells and skin fibroblasts of subjects with type 2 diabetes will be significantly shorter than those without type 2 diabetes, and age-related decline in telomere length will accelerate after the development of type 2 diabetes compared with controls.
(8) Telomere length in type 2 diabetes populations will be independently and inversely associated with the prospective risk of developing microvascular complications in type 2 diabetes, and with their rate of progression to sight-threatening diabetic eye disease and macroproteinuria.
(9) Incident cancer cases will increase sharply after incident diagnosis of diabetes cases in large cancer registries.
(10) Functional polymorphisms in telomere-maintenance genes will be independent contributors to: risk of type 2 diabetes; rates of beta cell failure in type 2 diabetes; the incidence and prevalence of diabetic nephropathy and diabetic retinopathy; and adverse vascular outcomes in type 2 diabetes.

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