RESEARCH ARTICLE

Diabetes - Increased Risk for Cancers through Chromosomal Aberrations?

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Abstract

Diabetes, a comprehensive genetic disease, is principally due to the deregulation of glucose levels in the blood. In addition to contemporary epidemiological studies, systematic substantiation suggests that long-term diabetes leads to cancers due to a variety of reasons. In this study, blood samples were collected with informed consent from confirmed type I diabetic (T1DM, n=25) and type II Diabetic patients (T2DM, n=25) with equal numbers of controls. Further depending on the lifestyle habits they were subdivided into smokers/non-smokers and alcoholics/non-alcoholics. Chromosomal assays were performed for these cases and it was found that there was a significant increase in chromosomal aberration frequency in diabetic patient groups who are exposed to smoking and alcohol than that of normal diabetic groups (T1DM and T2DM). On the other hand, patient groups who were non-smoking and non-alcoholics also showed higher chromosomal aberrations when compared to that of controls. While the mechanisms for these increased chromosomal aberrations in diabetic groups are not clear, they may be due to increased oxidative stress leading to oxidative damage and resulting in genomic instability, which in turn may contribute to an increased risk for cancer.

Keywords: Oxidative damage - diabetes - cancer - chromosomal aberrations - lifestyle habits

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Introduction

Diabetes and cancer are complicated and multiple subtyped diseases where the incidence is growing steadily globally. Liver, pancreas, endometrium, kidney, biliary tract, colon or rectum, prostate, breast, ovary, bladder cancer, and hepatocellular carcinoma are reported to be the most common cancers due to diabetes (Mitsuru et al., 2000; Edward et al., 2010; Liao et al., 2011; Jamal et al., 2011; Inal et al., 2012; Donovan et al., 2012; Xiong et al., 2012; Yang et al., 2013; Balasubramaniam et al., 2013). The hyperinsulinemia condition have been anticipated that it peaks the risk of liver cancer, as these individuals are more exposed to hepatic carcinogens, as decreased adenosine triphosphatase homeostasis in liver (Khan et al., 2006).

Several epidemiologic studies reported higher significant risk of cancer in diabetic patients and were 20% more in diabetic patients (Zendehdel et al., 2003; Hyun et al., 2013). Drug mediated oxidative stress is also known to be a major reason for tissue and organ toxicity (Damian et al., 2012), which may lead to various types of cancers. Certain metabolic inhibitor drugs like Metformin is reported to have no effect on cell division (Harman et al., 2012) but metformin strengthens tumorigenic nature either indirectly or by total decline in insulin levels (Pernicova and Korbonits, 2014). Oxidative stress may exhibit chromosomal instability, and amplification of these redox genes results in higher chromosomal instability (Charles and Erich, 2003). Earlier studies has shown that increased frequency of chromosomal aberrations results in high risk of developing cancers through different mechanisms like DNA damages and repair mechanisms (Obe et al., 2002). Diabetics are known to have an increased risk of renal cell carcinoma by 40% in both male and females. Also the metabolic syndromes like obesity and hypertension are the leading possible factors for renal cell carcinoma which are linked to diabetes mellitus (Satrudhan et al., 2012). Also studies has shown oxidative stress correlated with DNA damage (Cinkilic et al., 2009) in T2DM and T1DM patients and an increase in genomic instability in precancerous patients (George et al., 2014). Thus oxidative damage over time may cause genomic instability and may lead to cancers. Thus the risk of various cancers may increase in diabetic patients and on the other hand obesity, hyperglycaemia and increased oxidative stress lead to high cancer risk in diabetes. In this paper an attempt is made to correlate diabetes groups with cancer risk factors using chromosomal aberration assay.

Materials and Methods

Blood samples (2ml)were collected in heparinised vacutainers from confirmed T1DM, T2DM and controls from Medzon Diabetic centre, Vellore. Informed consent and ethical clearance was obtained for this study. T1DM

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(n=25) and T2DM (n=25) and an equal number of controls (n=25) were further classified into smokers/non-smokers and alcoholics/non-alcoholics in each group (Figure 1).

Methods

Chromosomal aberration assay was carried out for all the samples. Peripheral blood samples collected were cultured as follows. 0.5 ml of heparinised blood was added to 6 ml of RPMI (Hi Media), 1.2 ml of fetal bovine serum (Hi Media) and 0.3 ml of phytohemagglutinin (GIBCO®) and allowed for lymphocyte division upto 72 hours. CO_2 was released by unscrewing the culture vial cap for every 24 hours. At 72nd hour, cells were arrested by adding colchicine (0.6μg/ml) and treated with hypotonic solution (0.075M KCL). The cells were fixed on the microscope slides and stained with giemsa (4%) after air drying. Chromosome preparations were made by modified method of Hungerford, 1965. Well spread 100 metaphases were scored for chromosomal aberration assay.

Statistical analysis

For different data obtained from the patient groups and the control groups, Student's t-test was analysed using Graph pad prism 5 software. A p value of <0.05 with confidence limit of 95% was defined as statistically significant. Numerical data are presented as Mean±SE.

Results

The slides were analysed blindfold for chromosomal aberrations. In this study the diabetic patients were grouped as smokers/ alcoholics and non-smokers/ non-alcoholics for analyses. Interestingly in our study although we did not find any specific chromosome breaks, an increased random chromosomal aberrations in both the diabetic patient groups were observed. A drastic significant increase in chromosomal aberrations was observed in smokers/alcoholics in T1DM (1.4±0.42) and T2DM (2.8±1.16) when compared to controls (0.22±0.14) and diabetic groups with non-smokers (1.0±0.33) /non-alcoholics (1.2±0.31) (Table 1).

Table 1. The Chromosomal Aberration Frequencies in Diabetic Groups and Controls

Study Groups	Mean±SE
Controls	0.22±0.14
T1DM (non-smokers & non alcoholics) (p<0.05)	1.0±0.33
T1DM (smokers & alcoholics) (p<0.05)	1.4±0.42
T2DM (non-smokers & non alcoholics) (p<0.05)	1.2±0.31
T2DM (Smokers & alcoholics)v (p<0.05)	2.8±1.16

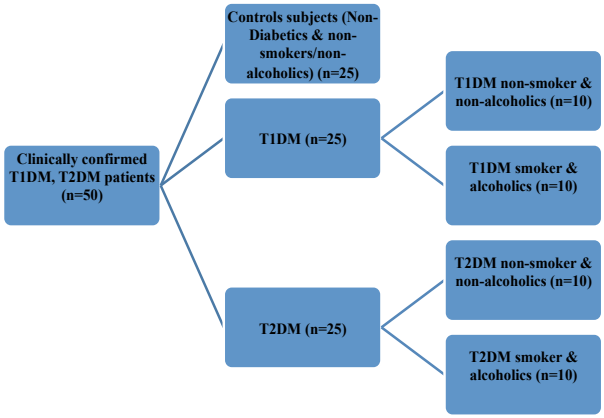

Figure 1. Patient groups

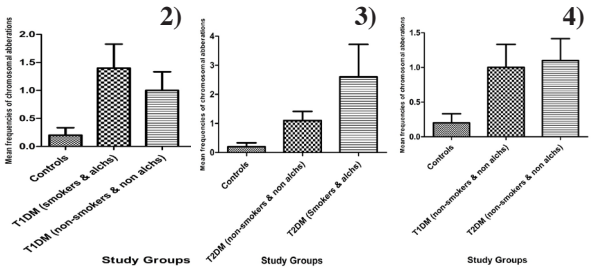

Figure 2,3,4. The Histograms Showing the Comparison of mean Frequencies of Chromosomal Aberrations between Different Patient Groups and Controls

Mean and standard errors were calculated for each group, student t- test showed 95% statically significant (p<0.05).

The histograms (Figures. 2, 3, 4) showing the comparison of mean frequencies of chromosomal aberrations between different patient groups and controls.

Discussion

An increase in cancer risk due to diabetes is documented but the underlying mechanism is not clearly understood till date. Although many risk factors are shared between cancers and diabetes patients, an increased oxidative stress is well documented which contribute to genomic instability (Limoli and Giedzinski, 2003) directly or indirectly. Also several studies reported an increased oxidative damage in diabetes patients using cytogenetic tests (Dominguez et al., 1998; Sardas et al., 2001; Cinkilic et al., 2009). However, they were inconclusive. In the present study, it is observed that a significantly high frequency of chromosomal aberrations in T1DM and T2DM indicates that diabetics may be at a higher risk for developing cancers than the control subjects (without diabetes). Chromosomal aberration assay may be used as a marker to evaluate the genomic instability in the lymphocytes of diabetes patients.

Recently Nefic and Handzic (2013) reported the DNA damage to be correlated with life style factors and micronuclei frequency in smokers. Our results also show an increase in chromosomal aberrations in smokers and alcoholics than that of controls (diabetics without smoking and alcoholics). As it is known that smoking and alcohol consumption triggers cancer (Goa et al., 2013; Shahdoust et al., 2013) this study also confirms that alcohol and smoking will increase the chances of cancer risk in these diabetic patients.

In conclusion, certain diabetic therapies were also found to be cytotoxic in nature and as literature shows medications (Bonnefond et al., 2013) could be one of the reasons for high chromosomal aberrations. This study has been extended to an in vitro study to assess the relationship between drugs and chromosomal aberrations, which may help in understanding the role of diabetes, drugs and cancers.

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