

Sera Anti-P53 Antibody Provides New Information Which Explains the Link Between Diabetes and Cancer

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Introduction: Abnormalities in glucose metabolism in diabetic patients may lead to an increased risk of certain cancers. Epidemiological studies and meta-analysis have shown that factors such as gender, age, obesity, and insulin resistance are related to cancer incidence. The anti-p53 antibody is a known cancer marker due to tumor-associated p53 accumulation. Many studies have aimed to unravel the link between diabetes and cancer. Here, we aimed to elucidate the impact of diabetes on malignancies by analyzing anti-p53 antibody in sera of type 2 diabetes mellitus (T2DM) patients.

Materials and Methods: We conducted an observational study with a cross-sectional design. A total of 149 subjects comprised of 78 T2DM patients (32 with cancer risk and 46 subjects without cancer risk), 51 T2DM patients with cancer, and 20 healthy subjects as controls from multisites. The anti-p53 antibody was measured by enzyme-linked immunosorbent assay, while HbA1c was measured using the NGSP standardized method.

Results: We observed an 8.3-fold ($p<0.05$) increase of anti-p53 antibody in the sera of T2DM patients and a 24-fold increase ($p<0.001$) in T2DM patients with cancer compared to healthy subjects. The anti-p53 antibodies significantly increased almost three times ($p<0.05$) in T2DM patients with cancer (0.72 U/mL \pm 0.20) compared to T2DM patients (0.25 U/mL \pm 0.05). Meanwhile, this antibody was almost undetectable in healthy subjects as a control group (0.03 U/mL \pm 0.03). The anti-p53 antibody level was higher in T2DM with cancer risk patients. However, we did not find a significant difference for it in T2DM without cancer risk patients (0.19 U/mL \pm 0.03) and T2DM with cancer risk patients (0.29 U/mL \pm 0.08). Multivariate regression analysis showed that T2DM with cancer was the only one independent factor ($\beta=0.218$, $p=0.019$) that could predict the increase of anti-p53 antibody, controlled by age, gender, BMI, DM duration, and HbA1c.

Conclusion: Our results showed that anti-p53 antibody almost not detected in healthy subjects, but 8.3-fold increase in the sera of T2DM patients and 24-fold increase in T2DM patients with cancer. Therefore, this biomarker provides new information which explains the link between diabetes and cancer.

Keywords: anti-p53 antibodies, P53, cancer, diabetes mellitus

Introduction

Diabetes is a metabolic disorder of multiple etiologies that is characterized by chronic hyperglycemia.¹ Hyperglycemia is associated with overall cancer risk in women and an increased risk of cancer at many sites in both genders.² Over the long term, poorly regulated metabolism in diabetes patients increases oxidative stress and upregulates the production of proinflammatory cytokines that may increase reactive oxygen species, which cause inflammation by reducing

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intracellular antioxidant activity.³ Cumulative data showed that chronic inflammation and systemic insulin resistance induced by hyperglycemia and excessive calorie intake are linked to the tumor suppressor activity.⁴ This calorie intake-tumor suppressor activity link could be also observed from another experiment that has found that cellular memory generated by prolonged exposure to oscillating glucose in endothelial cells can cause a detrimental condition, leading to the activation of p53 and its downstream pathways.⁵

Activation of p53 plays roles in regulating apoptosis, senescence, and DNA repair as well as in the regulation of glucose metabolism. Activation of p53 triggers induction of p53 upregulated mediator of apoptosis (PUMA), phosphatase and tensin homolog (PTEN),⁶ and its feedback inhibitor murine double minute oncoprotein (MDM2).⁷ In normal healthy cells, p53 is maintained at low levels by the E3 ubiquitin ligase MDM2, which ubiquitylates p53 and targets p53 for proteasomal degradation. In response to various stressors, phosphorylation of the amino terminus of p53 prevents interaction with MDM2, leading to p53 stabilization.⁸

Regarding the role of p53 in apoptosis and senescence, previous studies have suggested that p53 is mobilized to the mitochondrial membrane during oxidative stress induced by hyperglycemia, which leads to pancreatic β -cell apoptosis.⁹ The tumor suppressor p53 balances the glycolysis pathway and oxidative phosphorylation in producing ATP to help regulate metabolism. As a consequence, the tendency of cancer cells utilizing the glycolytic pathway to produce ATP is inhibited.⁸ It has recently been shown that p53 regulates glucose metabolism via p53-induced glycolysis and apoptosis regulator via TP53-inducible glycolysis and apoptosis regulator (TIGAR) and regulates insulin sensitivity via phosphatase and tensin homolog (PTEN). However, impaired glucose metabolism in diabetic patients leads to mitochondrial dysfunction and could notably inhibit p53. As a result, more elevated glucose circulating in the blood could activate several growth factors signaling. It is similar to the mechanism observed in mutant p53, of which positively regulates glucose uptake in cancer to use the glycolytic pathway as energy production more since there is a defect on oxidative phosphorylation.¹⁰

Interestingly, both *in vitro* and *in vivo* studies have shown that mutant p53 is correlated with increased AKT activity in some cancers.^{11,12} The accumulated mutant p53 protein is seen as an antigen that stimulates the formation of anti-p53 antibodies occurring in the sera of cancer

patients.¹³ The anti-p53 antibody has been used as a molecular marker to study target tissues or fluids, such as blood serum, in populations with high cancer risk, such as heavy smokers.¹⁴ Therefore, anti-p53 antibody could be a potential biomarker in cancer detection and correlates with several cancers.¹⁵

We are interested to know the effect of glucose blood concentration measured as HbA1c and the role of p53 towards cancer metabolism, especially in type 2 diabetes mellitus (T2DM). Thus, the present study was undertaken to investigate anti-p53 antibody serum levels in T2DM patients further.

Materials and Methods

Study Design

This was a cross-sectional study and already approved by The Ethics Committee, Faculty of Medicine, Universitas Indonesia—Dr. Cipto Mangunkusumo Hospital (No. 346/UN2.F1/ETIK/2017) and The Ethics Committee, Dharmais Cancer Hospital (No. 048/KEPK/VIII/2017). This study was conducted in accordance with the Declaration of Helsinki. We collected samples from April 2017 to January 2019 and all the patients was provided informed consent prior to sample withdrawal.

Subjects

Participants comprised 78 T2DM patients (with and without cancer risks) attending the Diabetes Polyclinic in two primary health center (Pasar Minggu and Cimanggis Primary Health Center) and two general hospitals (Depok and Tangerang General Hospital). The inclusion criteria for T2DM patients group were diabetes mellitus patients age ≥ 35 years,¹⁶ HbA1c $\geq 6.5\%$,¹⁷ and regular treatment with antidiabetic drugs for at least for 6 months. The 51 T2DM patients with cancer were patients from Dharmais Cancer Hospital. The exclusion criteria for T2DM patients with cancer group were severe anemia or a cancer diagnosis before T2DM diagnosis and in a chemotherapy session. For the control, we involved 20 healthy subjects. The inclusion criteria for healthy subjects group were normal HbA1c, normal blood pressure, BMI ≤ 30 kg/m², and not taking any medication for diabetes mellitus or hypertension. Patients' medical records were screened to assess the eligibility, and an interview was conducted to assure that participants met all of the criteria.

T2DM with cancer risk definition is T2DM patients with one or more cancer risk(s). Each patient's cancer risk

was determined by smoking habit, obesity, and family's cancer history. Based on this information, the participants were divided into three groups: T2DM patients, T2DM patients with cancer, and healthy subjects as control.

Sample Collection and Analysis

Blood samples were collected from all the participants, who were asked to refrain from consuming anything other than water for at least 8 hrs (fasting conditions). Blood was collected by a certified phlebotomist and transferred to a vacutainer serum tube. Samples were incubated at room temperature for 15–30 mins and then centrifuged at 1000–2000 rpm for 10 min in a refrigerated centrifuge to obtain serum. Serum was stored at -20°C until analysis. Serum anti-p53 antibody was analyzed using the enzyme-linked immunosorbent assay method (MESACUP Anti-p53 Test, Medical & Biological Laboratories Co. Ltd. (MBL), Nagoya, Japan). Whole blood samples for HbA1c analysis were taken from a peripheral vein and directly transferred to Afinion™ HbA1c Test Cartridge (Allere, USA) using a capillary pipe and then analyzed using Afinion™ AS100 Analyzer (Allere, USA).

Statistical Analysis

Descriptive statistics are presented on mean. For categorical variables, groups were compared using the chi-square test. The Kruskal–Wallis and Mann–Whitney *U*-tests were used to analyze non-parametric data, while ANOVA was used to analyze parametric data. Correlations between two variables were analyzed using the bivariate Pearson or Spearman test, depends on the normality of the data. Variables with $p < 0.25$ in correlation analysis with anti-p53 antibody (age, gender, BMI, DM duration, and HbA1c) were included in multivariate linear regression analysis. A *p*-value of less than 0.05 was considered statistically significant. SPSS version 20 was used to perform the analysis (IBM Statistic).

Results

Subject Characteristics

The basic characteristics of the study subjects were presented in Table 1. There were differences in several characteristics (age, body weight, body height) between T2DM patients and T2DM patients with cancer groups. Most of diabetic patients were overweight (BMI 25 to 29.9 kg/m^2), indicating that the elevated circulating of free fatty acids (FFAs) might decrease insulin-stimulated glucose uptake.¹⁸ The HbA1c level as

Table 1 Basic Characteristics of Study Subjects

Characteristic	T2DM Patients (78)	T2DM Patients with Cancer (51)	<i>p</i>	Healthy Subjects (20)
Gender			0.611	
Male	20 (25.6)	16 (31.4)		6 (30.0)
Female	58 (74.45)	35 (68.6)		14 (70.0)
Age (years)	58.97±7.70	50.08±7.64	<0.001**	55.20±7.13
BMI (kg/m^2)	26.16±4.46	22.75±3.79	<0.001**	23.68±3.37
Body Weight (kg)	63.48±10.70	58.58±11.70	0.006*	59.43±11.75
Body Height (cm)	155.88±6.94	160.16±7.13	0.001*	157.85±7.82
Diabetes	7.49±5.17	5.45±3.56	0.055	0 (0.00)
Duration (years)				
HbA1c (%)	8.82±1.97	7.02±1.45	<0.001**	5.38±0.30
Hypertension			0.002*	
Yes	36 (46.2)	9 (17.6)		0 (0.0)
No	42 (53.8)	42 (82.4)		20 (100.0)
Smoking Habit			0.013*	
Yes	11 (14.1)	0 (0.0)		0 (0.0)
No	67 (85.9)	51 (100.0)		20 (100.0)
Family's Cancer History			0.004*	
Yes	32 (41.0)	8 (15.7)		0 (100.0)
No	46 (59.0)	43 (84.3)		20 (0.0)

Notes: Data presented as n (%) or mean±SD; *p*, significance between T2DM Patients and T2DM Patients with Cancer; Independent *T*-test for normal distributed data, Mann–Whitney test for not normal distributed data, Chi-square test for categorical data. The statistically significant difference shown as *($p < 0.05$) and **($p < 0.001$).

seen in Table 2 were above the limit recommended for diabetes mellitus patients (HbA1c < 7%), which indicates the level of blood glucose was higher.¹⁷ Uncontrolled blood glucose promotes mitochondrial dysfunction that contributes to insulin resistance.¹⁹ Both impaired mitochondria and defect of insulin sensitivity could activate various signaling pathways, particularly in insulin signaling, and therefore induce cancer progression.²⁰

The number of participants in the T2DM patients without cancer risk was 32 and T2DM patients with cancer risk was 46. There were significant differences in term of gender, age, and duration of diabetes, instead of the risk cancer parameters (BMI, smoking habit, and family's cancer history).

There were no difference in gender proportion between T2DM patients group (20 male and 58 female) and T2DM patients with cancer group (16 male and 35 female). However, there was significant difference between number of men and women in T2DM patients with cancer risk group (17 male and 29 female) and T2DM patients

Table 2 Sub Analysis for T2DM Patients Group According to Cancer Risk: Basic Characteristics

Characteristic	T2DM Patients Without Cancer Risk (32)	T2DM Patients with Cancer Risk (46)	p
Gender			0.013*
Male	3 (9.4)	17 (37.0)	
Female	29 (90.6)	29 (63.0)	
Age (years)	61.94±6.03	56.91±8.12	<0.001**
BMI (kg/m ²)	24.12±2.62	27.59±4.93	<0.001**
Body Weight (kg)	57.71±7.28	67.49±10.93	<0.001**
Body Height (cm)	154.63±6.05	156.76±7.43	0.183
Diabetes Duration (years)	8.80±5.21	6.59±5.00	0.023*
HbA1c (%)	9.26±1.96	8.52±1.94	0.120
Hypertension			0.207
Yes	18 (56.3)	18 (39.1)	
No	14 (43.8)	28 (60.9)	
Smoking Habit			0.008*
Yes	0 (0.0)	11 (23.9)	
No	32 (100.0)	35 (76.1)	
Family's Cancer History			<0.001**
Yes	0 (0.0)	32 (69.6)	
No	32 (100.0)	14 (30.4)	

Notes: Data presented as n (%) or mean±SD; p, significance between T2DM patients without and with cancer risk; Independent T-test for normal distributed data, Mann-Whitney test for not normal distributed data, Chi-square test for categorical data. The statistically significant difference shown as *(p<0.05) and **(p<0.001).

without cancer risk group (3 male and 29 female) (p=0.013). Further, we put gender and other potential confounders (which has p<0.025 in bivariate analysis with antiP53-antibody, and found that T2DM with cancer status was the only one independent factor (beta=0.218, p=0.019) that could predict the increase of anti-p53 antibody, controlled by age, gender, BMI, DM duration, and HbA1c (Table 3).

Anti-P53 Antibody Levels

We discovered an 8.3-fold (p<0.05) increase of anti-p53 antibody in the sera of T2DM patients and a 24-fold increase (p<0.001) in T2DM patients with cancer compared to healthy subjects (Figure 1). The anti-p53 antibodies significantly increased almost three times (p<0.05) in T2DM patients with cancer (0.72 U/mL±0.20) compared to T2DM patients (0.25 U/mL±0.05). Meanwhile, this antibody was almost undetectable in healthy subjects as a control group

Table 3 Multivariate Linear Regression Analysis for Anti-P53 Antibody

Variable	R Square	Standardized Coefficients (Beta)	p
Crude Model	0.065		
Cancer Status		0.255	0.002*
Adjusted Model	0.103		
Cancer Status		0.218	0.019*
Age (years)		-0.100	0.295
Gender		-0.136	0.096
Body Mass Index (BMI) (kg/m ²)		-0.029	0.723
HbA1c (%)		-0.063	0.453
Diabetes Duration (years)		-0.009	0.923

Notes: Cancer status is ordinal scale (0=healthy subjects, 1=T2DM patients, 2=T2DM patients with cancer); gender is nominal scale (1=male, 2=female). The statistically significant difference shown as *(p<0.05).

(0.03 U/mL±0.03). However, we did not find a significant difference for anti-p53 antibody between T2DM without cancer risk patients (0.19 U/mL±0.03) and T2DM with cancer risk patients (0.29 U/mL±0.08) (Figure 2), which the highest values were 0.67 U/mL and 2.95 U/mL in T2DM patients without and with cancer risk, respectively. The mean value of anti-p53 antibodies were presented in mean±SEM. The positive serum antibodies (≥ 1.3 U/mL)²¹ were found 3% in T2DM patients and 10% in T2DM patients with cancer.

Multivariate regression analysis showed that T2DM with cancer was the only one independent factor (beta=0.218, p=0.019) that could predict the increase of anti-p53 antibody, controlled by age, gender, BMI, DM duration, and HbA1c (Table 3).

Discussion

Extensive studies have been conducted to unravel the links between diabetes and cancer.²² Several mechanisms, including abnormality of glucose homeostasis and insulin resistance, have been suggested to involve as risk factors in the development of cancer survival in diabetes mellitus patients.^{1,23} Tumor suppressor p53 has associated with having a significant impact in respect of diabetes and cancer progression. Aside from the guardian of the genome that controlling gene expression and promoting DNA repair, p53 also crucial in maintaining glucose homeostasis via regulation of glucose transporters.⁸ Previous study has shown that hyperglycemia induces mutagenesis in human lymphoblastoid cells, which suggests promoting the activation of oncogenic signaling.²⁴ It is also supported by

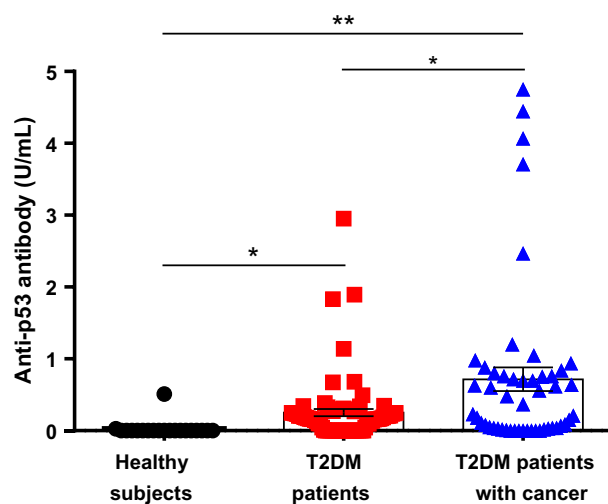


Figure 1 Anti-p53 antibody level in healthy subjects, T2DM patients, and T2DM patients with cancer. Values represent the mean of healthy subjects ($n=20$, $0.03 \text{ U/mL} \pm 0.03$), T2DM patients ($n=78$, $0.25 \text{ U/mL} \pm 0.05$), T2DM patients with cancer ($n=50$, 1 outlier was excluded, $0.72 \text{ U/mL} \pm 0.20$). The statistically significant difference shown as $*$ ($p < 0.05$) and $**$ ($p < 0.001$). Data presented as mean \pm SEM.

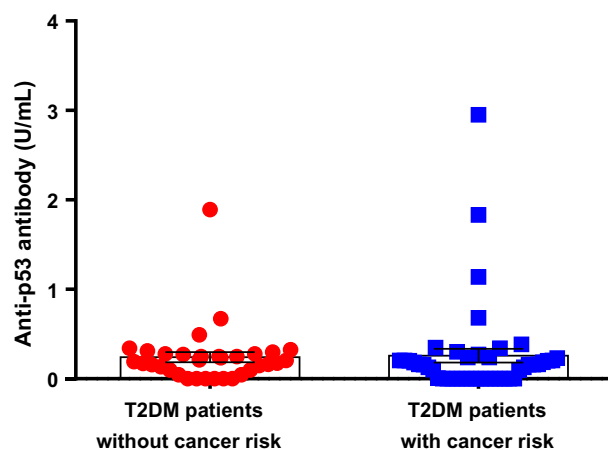


Figure 2 Anti-p53 antibody level in the sub group of T2DM patients according to cancer risk. Values represent the mean of T2DM without cancer risk patients ($n=32$, $0.19 \text{ U/mL} \pm 0.03$) and T2DM with cancer risk patients ($n=46$, $0.29 \text{ U/mL} \pm 0.08$) ($p=0.292$). Data presented as mean \pm SEM.

another study that found abundant serum of glucose and insulin enhances cell cycle progression, which attributes to cell proliferation.²⁵

High cytoplasmic p53 levels, whether mutant or wild-type, increased the likelihood of p53 protein being degraded by proteasomes and presented on cell surfaces, where T-cells recognize it in the major histocompatibility complex class I response to generate the p53 auto-antibody.²⁶ This antibody is a potential predictor of cancer survival because p53 mutation occurs widely in certain cancers.²⁷ Interestingly, we observed a 8.3-fold ($p < 0.05$) increase of anti-p53 antibody in the sera of T2DM patients and a 24-fold increase

($p < 0.001$) in T2DM patients with cancer compared to healthy patients. Moreover, this antibody was three times higher ($p < 0.05$) in T2DM patients with cancer than T2DM patients only. The positive serum antibodies ($\geq 1.3 \text{ U/mL}$) were found 3% in T2DM patients and 10% in T2DM patients with cancer. These percentages were quite smaller to indicate if there is an aberrant of p53 activity in T2DM patients. The anti-p53 antibody mostly detected in cancer patients with a prevalence range from 4–30%.²⁸ It also appears at a low level in autoimmune diseases and types 1 diabetes mellitus.²⁹ The anti-p53 antibody level was higher in T2DM with cancer risk, but we did not find a statistical difference when compared to T2DM without cancer risk. However the true risk factor could be something other than the suspected risk factor defined in this study. Though the anti-p53 antibody value relative low to accurately detect cancer mutation in T2DM patients, these increased trends explained that diabetes exposure correlates with a higher anti-p53 antibody related to cancer progression.

Mutant p53 plays a significant role in inducing glycolysis through the translocation of glucose transporter protein type 1 (GLUT1) to the plasma membrane, which produces energy for cancer cells where excess glucose is available.⁸ However, when glucose is restricted, autophagy occurs and leading to degradation of mutant p53.³⁰ The accumulation of mutant p53 in the cytoplasm is responsible for the inhibition of autophagy.³¹ Oxidative stress, the DNA damage response, and genome instability can cause autophagy deficiencies.^{32–34} Oxidative stress stimulates the activity of a signaling receptor that regulates many oncogenic pathways.³⁵ Autophagy deficiency in the liver is known to drive the progress of liver cancer through inflammation and chronic cell death.^{36,37}

Interestingly, there is increasing evidence that chronically elevated glucose in diabetes induces the accumulation of p53 in the cytosol that inhibits the autophagic clearance of damaged mitochondria by inhibitory protein-protein interactions with parkin, leading to impairment of mitochondrial energetics and subsequent insulin secretion signals in islet β -cells.³⁸ The inhibition of autophagy in human, mouse, and nematode cells is mediated by cytoplasmic p53, but not nuclear p53.³⁹ Hence, oxidative stress due to glucose abnormalities in type 2 diabetes may promote cancer progression directly through autophagy deficiency due to the accumulation of p53, which induces serum anti-p53 antibody production. By contrast, the role of autophagy in cancer cells varies by tissue. Some types of “autophagy addicted” cancers promote

tumor growth as an adaptation to stress.^{40–42} Although the role of autophagy in cancer is still poorly understood,⁴³ balancing autophagy signaling by limiting glucose intake may be of therapeutic value in type 2 diabetes patients with a risk of cancer.

The complexities and inconsistencies regarding p53 function and status depend on the presence of distinct cellular stressors, such as obesity and nutrition deprivation, as well as the cell type. There is also a limitation in isolating p53 from the patient to measure p53 status, whether its mutant or normal cells that made anti-p53 antibodies are detectable in T2DM patients. Measurement of insulin and insulin growth factor 1(IGF1-1) may be needed to describe the patient's condition more comprehensive. Therefore, additional molecular studies on the status of p53 are further needed.

Conclusion

Our results showed that anti-p53 antibody almost not detected in healthy subjects, but 8.3-fold increase in the sera of T2DM patients and 24-fold increase in T2DM patients with cancer. Therefore, this biomarker provides new information which explains the link between diabetes and cancer.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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