RESEARCH ARTICLE

Changes of Plasma Tumor Necrosis Factor α and C-Reactive Protein Levels in Patients with Hypertension Accompanied by Impaired Glucose Tolerance and their Clinical Significance

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Abstract

Background: Chronic inflammation could affect the occurrence and development of malignant tumors. To explore the levels of tumor necrosis factor α (TNF-α) and C-reactive protein (CRP) in patients accompanied by impaired glucose tolerance (IGT) and their clinical significance. Materials and Methods: A total of 210 patients hospitalized in Affiliated Hospital of Taishan Medical University from Jun., 2013 to Dec., 2014 were selected, in which 92 cases were accompanied by IGT. Meanwhile, 80 randomly-selected healthy people by physical examination were as the control. The levels of routine biochemical indexes, plasma TNF-α and CRP in all subjects were measured. Results: Both systolic and diastolic pressures in hypertension group and hypertension plus IGT group were significantly higher than in control group ($p<0.01$), but there was no statistical significance between these two groups ($p>0.05$). The levels of fasting plasma glucose (FPG) and blood glucose 2 h after taking glucose in hypertension plus IGT group were markedly higher than other groups ($p<0.01$). Homeostasis model assessment-insulin resistance (HOMA-IR), TNF-α and CRP contents were on the progressive increase in control, hypertension and hypertension plus IGT groups, but significant differences were presented among each group ($P<0.01$). Hypertension accompanied by IGT had a significantly-positive association with CRP, TNF-α, FPG and blood glucose 2h after taking glucose. Conclusions: The levels of plasma TNF-α and CPR in patients with hypertension accompanied by IGT increase significantly, indicating that inflammatory reaction in these patient increases, thus suggesting that these patients should be focused regarding cancer prevention.

Keywords: Hypertension - impaired glucose tolerance - C-reactive protein - tumor necrosis factor α

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Introduction

It is widely known that tumor necrosis factor-α (TNF-α) is important in promoting tumor growth and in the progression of cancers (Charles et al., 2009; Dobrzycka et al., 2009), due to the fact that TNF-α could stimulate cell growth and contribute to metastasis. Meanwhile, it is also suggested that serum C-reactive protein (CRP) could be an independent marker of development, progression and survival for cancers, eg., gastric, colorectal, pancreatic, hepatocellular, urological, ovarian cancer, as well as lymphoma, and osteosarcoma (Hashimoto et al., 2005; Karakiewicz et al., 2007; Koike et al., 2008; Pine et al., 2009; Shimura et al., 2012). Another common disease hypertension is associated with damage of the target organs like heart, brain and kidney. The relationship between TNF-α, CRP and hypertension has been well established (Ajmal et al., 2014). Various complications are very easy to appear when diabetes mellitus is accompanied, which severely decreases the patient's quality of life (Cuspidi et al., 2015). Impaired glucose tolerance (IGT), a special metabolic status between normal glucose tolerance and diabetes mellitus, is an early lesion of diabetes mellitus and may finally develop into diabetes mellitus if timely intervention is not applied (Hellgren et al., 2014). Abnormal glucose metabolism of IGT mainly manifests postprandial hypertension or not accompanied by increased fasting plasma glucose (FPG), which may induce hyperinsulinemia, promote oxidative stress and vascular inflammatory responses as well as dysfunction of endothelial cells.

The incidence of insulin resistance (IR) in patients with hypertension accompanied by IGT will increase dramatically. IR is a phenomenon that hepatocytes, adipocytes and muscular cells trigger an insufficient response to the insulin with normal concentration and an important reason for diabetes mellitus. It also plays a certain role in the formation of hypertension (Akande et al., 2013). The study revealed that IR was a chronic subclinical inflammatory process. The signal transduction

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of intracellular inflammatory responses mediated by inflammatory factors made the insulin receptor substrate serine in insulin sensitive cells phosphorylation so as to block the insulin signal transduction and induce IR (Daniele et al., 2013; Chang et al., 2014; Mauer et al., 2014). It is reported that chronic inflammation affects the occurrence and development of various malignant tumors and plays an important role in a lot of cancers, such as ovarian cancer. The researchers found that 27 genes involved in inflammatory response, and the correlation between their expression and tumorigenesis was analyzed. The results displayed that 5 genes were related to the occurrence of ovarian cancer, suggesting that alleviation of chronic inflammation may decrease the risk of tumorigenesis (White et al., 2012). In this study, the changes of CRP and TNF-α levels in patients with hypertension accompanied by IGT and their independent risk factors were analyzed to further explore the action of inflammation in occurrence, development and prognosis of hypertension accompanied by IGT and illustrate whether there was mutual promotion between hypertension accompanied by IGT and inflammatory cytokines.

Materials and Methods

Research objects

A total of 118 hypertensive patients and 92 cases of hypertension accompanied by IGT who all had complete clinical data and were hospitalized in Affiliated Hospital of Taishan Medical University from Jun., 2013 to Dec., 2014 were all selected as research objects. Inclusion criteria: (1) Meeting the diagnostic standards of Chinese Guidelines for Hypertension Prevention and Treatment in 2011; (2) FPG <6.1 mmol/L; (3) Conducting a standardized oral glucose tolerance test (OGTT, 75 g) first, and then the glucose levels of hypertensive patients and those with hypertension accompanied by IGT <7.8 mmol/L and being 7.8~11.1 mmol/L respectively 2h after OGTT; (4) Participating in this study voluntarily and signing informed consent forms, with better compliance. Patients with the following diseases were all excluded, including coronary heart disease, severe cardiac insufficiency or rheumatic valve heart disease, secondary hypertension, acute complications of hypertension or cerebrovascular disease, injured FPG, diabetes mellitus, hepatic insufficiency, serious active infectious disease, immunological disease and malignant tumors. Meanwhile, 80 healthy people by physical examination were as the control.

This clinical trial was conducted through strictly following the ethical principles of human body medical research in Declaration of Helsinki. Experimental protocols were approved by Ethics Committee of Affiliated Hospital of Taishan Medical University. All subjectswere told detailed experimental contents by researchers and signed informed consent form before enrollment.

Methods

Collection of general data: General data of all subjects were recorded, including the gender, age, smoking history, family history, previous history and history of administration. The height, body weight and blood pressure were routinely measured, and body mass index (BMI) was calculated. BMI=body weight (kg)/height2 (m^2).

Laboratory examination: The venous blood of all fasting subjects was drawn in the morning, and the levels of blood lipids, FPG, fasting insulin, CRP and TNF-α were detected. The venous blood was drawn again to detect the level of blood glucose 2h after the subjects orally took 75 g glucose. Both blood lipids and glucose were detected using AU680 automatic biochemical analyzer (Beckman Coulter Commercial Enterprise Co., Ltd., China). Glucose oxidase method and radioimmunoassay (human serum insulin radioimmunoassay kit, Shenzhen Ailawen Biotech Co., Ltd.) were respectively applied to detect the blood glucose and insulin. TNF-α was detected by double antibody sandwich enzyme-linked immunosorbent assay (ELISA) (TNF-α detection kit, American Endogen Company) and CRP by rate nephelometry (Beckman Array 360 system full-automatic microprotein analyzer and its supplementary reagents). Homeostasis model assessment (HOMA) was used for IR assessment. HOMA-IR=FPG (mmol/L)×fasting insulin (U/L)/22.5.

Statistical data analysis

SAS 9.3 software package was used for data analysis.

Table 1. Comparison on the General Data and Routine Biochemical Indexes of Each Group (x±s)

Items	Control group	Hypertension group	Hypertension plus IGT group	F or χ^2	*P*
Age (year)	62.07±5.73	60.92±6.15	61.42±6.08	0.8725	0.4190
Gender (male/female)	48/32	63/55	55/37	1.2067	0.5470
BMI (kg/m^2)	24.07±2.13	24.41±2.66	24.19±2.08	0.5395	0.5836
Systolic pressure (mmHg)	122.88±10.03	159.29±9.11**	161.46±9.85**	439.412	0.0000
Diastolic pressure (mmHg)	74.97±8.61	95.06±9.31**	97.26±10.17**	146.433	0.0000
TC (mmol/L)	4.37±0.49	4.41±0.74	4.28±0.51	1.1973	0.3035
TG (mmol/L)	1.58±0.52	1.71±0.62	1.73±0.57	1.7000	0.1845
LDL-C (mmol/L)	2.59±0.36	2.69±0.39	2.66±0.34	1.7999	0.1672
HDL-C (mmol/L)	1.61±0.18	1.55±0.11	1.58±0.19	1.7455	0.1764
FPG (mmol/L)	4.89±0.31	5.01±0.43	5.41±0.22**##	56.8410	0.0000
Glucose 2 h after taking glucose (mmol/L)	5.56±0.37	5.49±0.26	9.39±0.71**##	2092.22	0.0000
HOMA-IR	1.34±0.29	1.87±1.15**	3.91±1.74**##	109.232	0.0000

*Compared with control group, **P<0.01; Compared with hypertension group, ## P<0.01, Comparison on the levels of plasma CRP and TNF-α of each group

Table 3. Analysis on the Factors Related to Hypertension Accompanied by IGT

Risk factors	B	Wald value	P value	OR	95%CI
FPG	0.622	10.166	0.002	1.364	1.089~2.430
Glucose 2 h after taking glucose	0.070	13.017	0.000	1.148	1.006~1.301
CRP	1.027	3.463	0.025	3.106	1.059~7.978
TNF-α	1.305	4.819	0.028	3.427	1.175~9.462

Table 2. Comparison on the Levels of Plasma CRP and TNF-α of Each Group (x±s)

Groups	CRP (mg/L)	TNF-α (ng/mL)
Control group	5.91±1.42	22.19±11.24
Hypertension group	7.21±2.07**	28.91±12.07**
Hypertension plus IGT group	12.39±2.16**##	35.74±13.11**##
F	281.018	26.489
P	0.0000	0.0000

Compared with control group, **p<0.01; Compared with hypertension group, ## p<0.01, Analysis on the factors related to hypertension accompanied by IGT

Measurement data were tested by normality test, and those with normal distribution were expressed with the mean±standard deviation (x±s). t test was used for comparison between two groups, and one-way analysis of variance for comparison among groups. Enumeration data were tested by χ^2 test, expressed with percentages. Multi-factor Logistic regression analysis was applied to analyze the factors related to hypertension accompanied by IGT. All statistical tests were adopted two-sided tests, with α=0.05 as an inspection level.

Results

Comparison on the general data and routine biochemical indexes of each group

There was no statistical significance among three groups regarding the age, gender, BMI and levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) (p>0.05). Both systolic and diastolic pressures in hypertension group and hypertension plus IGT group were significantly higher than in control group (p<0.01), but there was no statistical significance between these two groups (p>0.05). The levels of FPG and blood glucose 2h after taking glucose in hypertension plus IGT group were markedly higher than other groups (p<0.01). HOMA-IR was on the progressive increase in control, hypertension and hypertension plus IGT groups, and significant differences were presented among each group (p<0.01) (Table 1).

Both CRP and TNF-α contents were on the progressive increase in control, hypertension and hypertension plus IGT groups, and significant differences were presented among each group (p<0.01) (Table 2).

Multi-factor Logistic regression analysis was conducted with hypertension accompanied by IGT as the dependent variable and CRP, TNF-α, FPG, blood glucose 2h after taking glucose, diastolic and systolic pressures as independent variables. The results showed that hypertension accompanied by IGT had a significantly-positive association with CRP, TNF-α, FPG and blood glucose 2h after taking glucose (Table 3).

Discussion

85% cancers originate from chronic inflammatory stimulation, and the mechanism may be related to inflammation-induced reduplicative necrosis, regeneration and proliferation of cells as well as various cytokines and reactive oxygen species produced by inflammatory cells (Chen et al., 2013; Chen et al., 2013; Qian et al., 2014; Xiao et al., 2014). The study displayed that a great many inflammatory diseases like inflammatory bowel disease could increase the risk of tumorigenesis, but for the tumor not conspicuously related to inflammation from the perspective of epidemiology, activation of oncogenes could result in generation of inflammatory molecules and aggregation of inflammatory cells. Nuclear molecules of inflammatory cells in tumor microenvironment can affect every step of tumor progression, including migration of tumor cells (Mantovani et al., 2009). Some cytokines, such as interleukin and TNF, can activate inflammation and enhance the migration of tumor cells through action on some steps like cell dissemination and plantation in secondary parts.

As a non-glycosylated protein, CRP stimulates the synthesis of hepatic epithelial cells in the occurrence of inflammation by mediation of inflammatory lymphokine interlukin-6 and TNF. As a typical acute phase reactant, CRP is the most well-known cardiovascular biological markers, and circulating CRP is used to predict the cardiovascular events in clinic. Additionally, it can accurately evaluate whether an individual is in a middle-risk population (Hage, 2013). Studies demonstrated that chronic inflammation and endothelial dysfunction might be related to hypertension and cardiovascular disease. CRP level was on the progressive rise in healthy people, patients with early hypertension and those with hypertension. Multivariate analysis revealed that CRP was an independent risk factor of hypertension (Wang et al., 2011; Zhang et al., 2014). The study showed that CRP could not only result in vasoconstriction by stimulating endothelial cells and other inflammatory cells to secrete TNF-α, endothelin-1 and vasoconstrictive peptides, but also promote the thickness of endangium via promotion

of vascular endothelial proliferation and migration, consequently leading to increased vascular resistance and progression of hypertension (Tsounis et al., 2014; Tosu et al., 2014).

TNF-α which is produced by activated macrophages and T cells can promote the expression of angiotensinogen in the liver to exert a regulatory effect on blood pressure by stimulating vascular smooth muscle cells to secret a large amount of endothelin (Lee et al., 2009). Bautista et al. found that TNF-α level in patients with hypertension was significantly higher than those with normal blood pressure, suggesting that TNF-α is an independent risk factor of increased blood pressure (Bautista et al., 2005). The reasons may be that reduced endothelial nitric oxide synthase and nitric oxide, weakened hemangiectasis and increased endothelin expression produced by action of TNF-α on endothelial cells lead to proliferation of vascular smooth muscle cells, thickened tube walls, shrunken lumens and increased peripheral resistance (Zhang et al., 2014). Additionally, TNF-α can also induce IR via inhibition of insulin signal transduction and enhancement of lipolysis and glycogen synthesis (Plomgaard et al., 2007). However, Obuchowicz et al believed that among the obese population, there was no statistical significance between hypertensive patients and those with normal blood pressure in terms of TNF-α level (Obuchowicz et al., 2014).

In conclusion, both CRP and TNF-α belong to proinflammatory cytokines with extensive biological activity and play important roles in the mediation and regulation of immune and inflammatory responses. They can not only promote the occurrence and progression of hypertension, but also lead to damage of pancreatic β cells, closely associated with diabetes mellitus. In this study, the levels of CRP and TNF-α were on the progressive increase in control, hypertension and hypertension plus IGT groups, and the results of multivariate regression analysis revealed that hypertension accompanied by IGT had a significantly-positive association with CRP and TNF-α, indicating that inflammatory reaction in the patient's body increases, thus suggesting that these patients should be focused regarding cancer prevention.

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