

Association between diabetes mellitus, hypertension, hyperlipidemia, chronic viral hepatitis, and the risk of multiple myeloma: a case-control study

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Abstract

Objective This case-control study aimed to investigate whether diabetes mellitus (DM), hypertension, hyperlipidemia, and chronic viral hepatitis are risk factors for multiple myeloma (MM). Moreover, the clinical characteristics of MM patients with or without the abovementioned exposure factors were analyzed.

Methods In total, 340 MM patients and 680 patients with benign diseases who were hospitalized from January 2012 to December 2017 were classified under the case group and control group, respectively. Data about medical history of DM, hypertension, hyperlipidemia and chronic viral hepatitis were collected by reviewing medical records. Univariate and multivariate analyses were conducted to compare the history of DM, hypertension, hyperlipidemia, and viral hepatitis between the two groups. Considering DM, hypertension, hyperlipidemia, and chronic viral hepatitis as exposure factors, clinical characteristics, such as renal function and presence of fungal and other types of infections, between the exposed and non-exposed groups were analyzed.

Results No significant difference was observed in the prevalence of DM, hypertension, and hyperlipidemia between the case and control groups. MM patients had a higher prevalence of chronic viral hepatitis than those with benign diseases. No significant difference was observed in the prevalence of renal dysfunction, fungal infection, and non-fungal infections in MM patients with or without DM, hypertension, and hyperlipidemia. MM patients with chronic viral hepatitis had a significantly higher prevalence of non-fungal infections during hospitalization than those without.

Conclusion No significant association was noted between MM and DM, hypertension, and hyperlipidemia. Chronic viral hepatitis is correlated to a significantly higher risk of MM, and MM patients with chronic viral hepatitis were more susceptible to non-fungal infections during hospitalization. Although a non-significant trend was observed in this study, we believe that DM and hypertension might be associated with a higher risk of MM. Thus, large-scale studies must be conducted to validate the results of the current study.

Key words: multiple myeloma (MM); diabetes mellitus (DM); hypertension; hyperlipidemia; chronic viral hepatitis; case-control study

Received: 12 November 2019
Revised: 20 December 2019
Accepted: 28 February 2020

Multiple myeloma (MM) is a malignant disease characterized by clonal plasma cell proliferation and is the second most prevalent blood cancer. Moreover, this condition is incurable among elderly individuals [1]. The common clinical manifestations of MM include bone pain, anemia, renal insufficiency, infection, and hypercalcemia. The incidence of MM in China is about 1 per 100 000 population, which is lower than that in western countries. However, with the aging population,

its incidence increases annually. The etiology of MM is not fully understood, and specific cytogenetic abnormalities, such as t(4;14), t(14;16), t(14;20), 1q+, 1p– and 17p–, are considered the molecular risk factors of this condition. Studies have shown that microRNA-32 may play an important role in the development of MM [2]. Moreover, clinical epidemiological studies have shown that the risk factors of MM may include pesticide exposure, radiation, obesity, viral infections [3–6], frequent consumption of

pickled foods, including sauerkraut, and experiencing negative life events^[7].

Hyperglycemia, hypertension, and hyperlipidemia are often referred to as the “three high”. In recent years, researchers have shown increasing attention to the relationship between these conditions and malignant tumors. Some studies conducted in other countries have shown that diabetes mellitus (DM) may be a risk factor of MM. In addition, DM may be associated with a higher risk of monoclonal gammopathy of unknown significance (MGUS) converting to MM and may lead to poor prognosis in MM patients^[8]. Chronic hepatitis is extremely common in China. Some researchers believe that individuals with chronic viral hepatitis may have a higher risk of hematological malignancies. Through a systematic search of literature in the database, we found that no study has assessed the association between the three high and the risk of MM in China. In addition, the correlation between chronic viral hepatitis and the incidence of MM has not been clearly reported. Therefore, this case-control study aimed to explore whether DM, hypertension, hyperlipidemia, and chronic viral hepatitis are risk factors for the onset of MM based on interviews and the case data of 340 MM patients and 680 patients with benign diseases who were matched according to age, gender, and admission year. In addition, in MM patients with or without the above-mentioned exposure factors, clinical characteristics, such as renal function, fungal infections, and non-fungal infections, were analyzed and compared to explore whether they are relevant and can be used as reference for the clinical prevention and treatment of MM.

Patients and methods

Patients

In this study, 340 MM patients admitted to Department of Hematology, Zhongnan Hospital of Wuhan University (China) from January 2012 to December 2017 were included in the case group. Meanwhile, patients of the same age, gender, and admission year who were admitted to the hospital due to benign diseases were classified under the control group with 1:2 pairs. Clinical data, including gender; age; history of hypertension, DM, hyperlipidemia, and viral hepatitis; presence of co-infection with fungal and non-fungal infections; and renal insufficiency, were collected.

As judgement might be affected, patients who did not meet the abovementioned criteria but presented with malignant tumors, other endocrine diseases, or mental diseases at a young age and those with incomplete data were excluded.

Diagnostic criteria

1. Multiple myeloma: in accordance with the Chinese MM Guidelines for Diagnosis and Treatment (revised in 2017)^[9].

2. Hypertension: mean systolic blood pressure ≥ 140 mmHg or mean diastolic blood pressure ≥ 90 mmHg or intake of antihypertensive drugs (according to the 2010 Chinese Guidelines for the Prevention and Treatment of Hypertension)^[10].

3. Hyperlipidemia, defined as meeting at least one of the following criteria: total cholesterol level ≥ 6.22 mmol/L, low-density lipoprotein cholesterol level ≥ 4.14 mmol/L, and triglyceride level ≥ 2.25 mmol/L (according to the 2016 Guidelines for the Prevention and Treatment of Dyslipidemia in Chinese adults)^[11].

4. Diabetes mellitus: (1) Symptoms of DM and random blood glucose level ≥ 11.1 mmol/L (random blood glucose defined as blood glucose assessed at any given time). The common symptoms of DM include polyuria, thirst, and weight loss without other causes. (2) Fasting blood glucose level ≥ 7.0 mmol/L (fasting status defined as no caloric intake for at least 8 h). (3) Blood glucose level ≥ 11.1 mmol/L based on a 2-h oral glucose tolerance test. The test was still performed as required by the World Health Organization. (4) Without the symptoms of DM but meeting one of the abovementioned criteria. A diagnosis of DM was made if one of the three criteria was still met during consultation on the next day (diagnostic criteria for DM proposed by the American Diabetes Association Standards of Medical Care in Diabetes-2019)^[12].

5. Chronic viral hepatitis: Hepatitis B, refer to the Guidelines of Prevention and Treatment for Chronic Hepatitis B (2019 version)^[13]. Hepatitis C, meet the Guidelines for the Prevention and Treatment of Hepatitis C (2019 version)^[14].

Statistical analysis

The R3.5.2 software (Mathsoft, USA) was used for analysis. Using Fisher's exact test and the Cochran-Mantel-Haenszel test, a univariate analysis was performed to assess differences in the history of exposure to DM, hypertension, hyperlipidemia, and viral hepatitis between the case group and control group after the stratification of variables, such as age, gender, and admission year. A multivariate logistic regression analysis was performed to analyze the abovementioned factors. The Fisher's exact test was used to compare the prevalence of renal dysfunction, fungal infections, and non-fungal infections among MM patients with or without the abovementioned exposure factors. A P value < 0.05 was considered statistically significant.

Results

Comparison of the exposure state of DM, hypertension, hyperlipidemia, and chronic viral hepatitis in MM patients and those with benign diseases

Among the 340 MM patients, 197 were men and 143 women, with a median age of 62.5 (24–89) years. Moreover, 45 (13.2%), 77 (22.6%), 5 (1.5%), and 18 (5.3%) MM patients presented with DM, hypertension, hyperlipidemia, and chronic viral hepatitis, respectively. Meanwhile, there were 680 patients with benign diseases. Among them, 394 were men and 286 women, with a median age of 62.5 (24–89) years. Moreover, 80 (11.8%), 128 (18.8%), 14 (2.1%), and 5 (0.7%) patients presented with DM, hypertension, hyperlipidemia, and chronic

viral hepatitis. The exposure rate of chronic viral hepatitis in the case group was significantly higher than that in the control group, and other exposure factors were not significantly different between the two groups (Table 1).

Comparison of renal dysfunction and presence of fungal or non-fungal infections during hospitalization among MM patients with or without the abovementioned exposure factors

MM patients with chronic viral hepatitis were found to have a significantly higher incidence of non-fungal infections during hospitalization than those without [odds ratio (OR) = 4.2, $P = 0.01$]. The trend of renal dysfunction and fungal infections increased during hospitalization in MM patients with diabetes compared with those without. However, the difference was not statistically significant

Table 1 Association between myeloma and diabetes, hypertension, hyperlipidemia, and viral hepatitis

Exposures		Subjects ($n = 1020$)		Unstratified analysis			Stratified by age		
		Myeloma	Control	OR	95% CI	P^*	OR	95% CI	P^{**}
Diabetes	Yes	45	80	1.14	[0.76, 1.72]	0.54	1.15	[0.77, 1.70]	0.56
	No	295	600						
Hypertension	Yes	77	128	1.26	[0.90, 1.76]	0.16	1.28	[0.92, 1.78]	0.16
	No	263	552						
Hyperlipidemia	Yes	5	14	0.71	[0.20, 2.11]	0.63	0.71	[0.25, 1.99]	0.68
	No	335	666						
Chronic viral hepatitis	Yes	18	5	7.53	[2.66, 26.2]	< 0.01	7.55	[2.78, 20.5]	< 0.01
	No	322	675						

Exposures		Stratified by gender			Stratified by year			Multivariate analysis		
		OR	95% CI	P^{**}	OR	95% CI	P^{**}	OR	95% CI	P^{***}
Diabetes	Yes	1.14	[0.77, 1.69]	0.57	1.14	[0.77, 1.69]	0.57	1.12	[0.75, 1.67]	0.59
	No									
Hypertension	Yes	1.26	[0.92, 1.74]	0.17	1.26	[0.92, 1.74]	0.18	1.30	[0.94, 1.81]	0.15
	No									
Hyperlipidemia	Yes	0.71	[0.25, 1.99]	0.68	0.71	[0.25, 1.98]	0.68	0.67	[0.24, 1.89]	0.45
	No									
Chronic viral hepatitis	Yes	7.53	[2.77, 20.5]	< 0.01	7.42	[2.75, 20.0]	< 0.01	7.83	[2.88, 21.3]	< 0.01
	No									

Note: OR: odds ratio; 95% CI: 95% confidence interval; P^* : P -value by Fisher's exact test; P^{**} : P -value by Cochran-Mantel-Haenszel test; P^{***} : P -value by multivariate logistic regression analysis

Table 2 The relationship between exposure factors and complications during hospitalization in MM patients

Complications during hospitalization		Exposure factors											
		Hypertension			Diabetes			Hyperlipidaemia			Chronic viral hepatitis		
		Yes	No	<i>P</i>	Yes	No	<i>P</i>	Yes	No	<i>P</i>	Yes	No	<i>P</i>
Renal dysfunction	Yes	14	33	0.26	10	37	0.10	0	47	1.00	1	46	0.49
	No	63	230		35	258		5	288		17	276	
Fungal infection	Yes	6	25	0.82	6	25	0.27	0	31	1.00	3	28	0.22
	No	71	238		39	270		5	304		15	294	
Non-fungal infection*	Yes	30	130	0.12	22	138	0.87	2	158	1.00	14	146	0.01
	No	47	133		23	157		3	177		4	176	

Note: *: Fungal and chronic hepatitis virus infections are not included

($P > 0.05$). MM patients with chronic viral hepatitis are at increased risk of fungal infections. No statistically significant association was observed between other exposure factors and comorbidities (Table 2).

Discussion

In recent years, the incidence of hyperglycemia, hypertension, and hyperlipidemia is increasing. According to the International Diabetes Federation (IDF) statistics, the number of DM patients worldwide reached 415 million in 2015. China has the highest number of DM patients globally, with 151 million recorded cases [15]. According to the data published on October 25, 2017, after adjusting for age and gender, the prevalence rate of hypertension in China is 37.2%. That is, 517 million people present with hypertension. The incidence rate of hyperlipidemia is extremely high, reaching up to 95%, among individuals aged > 65 years. The conditions associated with the three high are not only limited to vascular, nerve, and skin lesions, and several studies in China and other countries have confirmed that the three high is also closely correlated to malignant tumors. The American Diabetes Association and the American Cancer Association jointly issued a statement that DM is a risk factor for multiple types of malignant tumors, such as lung, colorectal, and breast tumors. Meanwhile, a history of DM is associated with a higher mortality from cancer. Individuals with malignant tumors had a higher risk of DM than those without [16]. Moreover, the incidence of DM varies among patients with different types of tumors. In a study of 205 type 2 DM patients with malignant tumors, gastrointestinal tumors accounted for 46.9% of all tumors, followed by hematologic tumors (26%) [17]. In a study by Tan LL *et al*, gastrointestinal tumors are the most common malignant tumors in patients with DM, followed by hematological and lung tumors [18]. The abovementioned studies have indicated that DM is closely correlated to hematologic malignancies. DM can increase the incidence of diffuse large B-cell lymphoma by 1.41 times [19]. MM is a malignant blood disorder. What is the correlation between DM and MM? Currently, no study in China has assessed this association.

Several scholars believe that hypertension and malignant tumors are both proliferative lesions with a similar pathogenesis. Therefore, hypertension may promote the development of malignant tumors [20]. Its mechanism may be correlated to the overexpression of cellular oncogenes in hypertension, low-level inflammation, insulin resistance, insulin-like growth factor, and the renin-angiotensin system. Hyperlipidemia is considered a susceptible factor and is associated with the pathology of cancer. Fat catabolism in the body produces free radical compounds with extra electrons,

which can increase the activity of carcinogens and cause cancer [21]. However, there is no study in China showing that hypertension and hyperlipidemia are associated with hematological malignancies. In this study, the incidence of DM (13.2%) and hypertension (22.6%) in the case group was slightly higher than that in the control group, and the incidence of hyperlipidemia (1.5%) was lower in the case group than in the control group. Although the difference was not statistically significant, individuals with diabetes and hypertension are more likely to have an increased risk of MM. Studies conducted in different regions have shown that DM is associated with the development of hematological tumors. Moreover, studies in other countries have revealed that IgA MM can occur secondary to hyperlipidemia [22]. Thus, to obtain more accurate epidemiological data of the three high in MM patients, multicenter and cross-regional prospective studies must be conducted in the future.

China has a high incidence of hepatitis. That is, the incidence of chronic viral hepatitis is always leading in class A and B infectious diseases in China [23]. From 2004 to 2013, the average annual incidence of hepatitis B infection was 72.61 per 100 000 population, and that of hepatitis C was about 15.51 per 100 000 population. An insufficient understanding of the immune mechanism of hepatitis infections has restricted the development of clinically effective interventions [24]. After the occurrence of the disease, it may gradually develop into hepatic cell carcinoma, which has an extremely high mortality rate. Moreover, studies in the literature have reported that hepatitis C is correlated to the development of hematological tumors. Nieters *et al* have conducted large, multi-center controlled studies that included 1807 patients with newly diagnosed malignant lymphoid diseases, and results showed that the risk of B-cell non-Hodgkin lymphoma and large B-cell lymphoma in hepatitis C virus RNA(+) patients was two and three times higher than that in normal individuals, respectively [25]. A Swedish cohort study has shown that the risk of MM is significantly higher in individuals with hepatitis C [26]. In the study by Wang LR *et al*, the incidence rate of hepatitis B was higher in MM patients than in healthy individuals [27]. The results of these studies are consistent with those of our study. That is, the incidence of chronic viral hepatitis in MM patients is significantly higher than that in the general population. Recent studies have shown that viral infection plays multiple roles in the process of carcinogenesis by causing an increase in genomic instability, cancer-promoting genetic mutations, signal pathway interruption, and tumor suppressor gene inhibition [28]. Meanwhile, hepatitis virus is a chronic antigenic stimulus to the body, which can cause immune system disorder and, subsequently, lymphocyte malignant proliferative diseases. Thus, this mechanism may be

responsible for the association between viral hepatitis and MM. Hepatitis is often in the state of inapparent infection in MM patients, and this process may also directly lead to MM [29]. No study has assessed the correlation between MM and hepatitis D and E in China and other countries. However, Pavlova and other scholars have reported that patients with blood diseases, particularly those with hematological malignancies, are more likely to develop hepatitis G than the general population [30].

What factors affect the clinical characteristics of MM patients? Studies have shown that MM patients are at risk of bacterial infections during hospitalization. At this period, combined DM, hospitalization time of 20 days, and high tumor stage based on the International Staging System are the independent risk factors of infections in MM patients [31]. A clinical study of 164 patients has shown that elevated creatinine and decreased serum albumin levels are independent risk factors for poor prognosis among MM patients [32]. Our study compared the clinical characteristics of MM patients with or without DM, hypertension, hyperlipidemia, and chronic viral hepatitis, and results showed that there is no significant difference in the prevalence of renal dysfunction, fungal infections, and other infections in MM patients with or without DM, hypertension, and hyperlipidemia. However, MM patients with DM are more likely to develop renal dysfunction and fungal infections during hospitalization. MM patients with chronic viral hepatitis have a significantly higher incidence of non-fungal infections during hospitalization than those without (OR = 4.2, $P = 0.01$), and the trend in the incidence of fungal infections has also increased. This result may be correlated to viral hepatitis, particularly in individuals with severe hepatitis who have impaired liver function and low immune function, which results in weak resistance and increased susceptibility to pathogens. By contrast, MM patients with viral hepatitis will have a longer hospital stay and more contact with pathogenic bacteria and medical staff, which lead to a higher risk of nosocomial infections. To date, no study has assessed the incidence of other infections in MM patients with chronic viral hepatitis in China and other countries.

In conclusion, individuals with DM and hypertension have an increased risk of MM. Thus, large-scale prospective studies must be conducted to validate the results of our study. Moreover, chronic viral hepatitis significantly increased the risk of MM. MM patients with chronic hepatitis are a special group with a significantly increased incidence of other infections. Hence, the replication of hepatitis virus must be closely monitored, and the prognosis of MM should be improved by preventing viral infection and providing antiviral treatment.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-019-0391-1

Cite this article as: Zhou G, Meng XY, Liu SQ. Association between diabetes mellitus, hypertension, hyperlipidemia, chronic viral hepatitis, and the risk of multiple myeloma: a case-control study. Oncol Transl Med, 2020, 6: 87–92.