Original Article

Relationship between the risk factors of cardiovascular disease by testing biochemical markers and young men with erectile dysfunction: a case-control study

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Background: Erectile dysfunction (ED) shares common risk factors with cardiovascular disease (CVD), such as diabetes mellitus (DM) and dyslipidemia, but the relationship between the risk factors of CVD in biochemical markers and young men with ED age 20–40 years is not fully clarified.

Methods: A total of 289 ED outpatients (20–40 years old) were allocated under ED group, based on patients' complaints and physical examinations. According to the frequency matching ratio of 1:4, 1,155 male individuals (20–40 years old) without ED were set as control group. All participants were tested for lipid profiles including total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), blood glucose (BG), homocysteine (HCY), liver function including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and renal function including uric acid (UA) and creatinine (CR). The study was designed to compare the two groups using an established binary logistic regression analysis model. The ED group was then subdivided into a younger ED group (20–30 years old) and an older ED group (31–40 years old) for further comparisons.

Results: After comparison, no obvious differences were found in medians of age, TC, TG, HDL, HCY, UA, and ALT in the two groups. Median LDL, BG, and CR were significantly higher and AST was much lower in the ED group ($P<0.01$). In binary logistic regression analysis, odds ratios (OR) for LDL, BG, CR, and AST were 1.279, 1.237, 1.026, and 0.978, respectively. The sensitivity value and specificity value were 43.25% and 72.56%, respectively. The medians of LDL, TG, and TC were higher and HDL was much lower in the older ED group, as compared with the younger group ($P<0.05$). No significant differences were displayed in medians of other biochemical markers in the above comparisons.

Conclusions: Elevated LDL, BG, and CR were related factors of ED in young men. Lipid profile was significantly different between young men with ED aged 20–30 and 31–40 years.

Keywords: Erectile dysfunction (ED); lipid profile; case-control study

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Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain and/or maintain an erection sufficient to permit satisfactory sexual performance (1). The multinational men's attitudes to life events and sexuality study showed that the prevalence of ED was 16% in men, generally, and approximately 9.52% in young men aged 20–40 years (2).

Moreover, amongst patients with new onset of ED, one in four was younger than 40 years old, and almost 50% of these young men complained of severe ED (3). The percentage of young men presenting to the clinic for ED has increased from 5% to over 15% from 2010 to 2015 (4). Recent research holds that the prevalence of ED in the current population could be as high as 30% (5).

The pathophysiology of ED may be physiologic (organic) and/or psychogenic. In the past, many young cases were thought to be psychogenic in nature. Studies have identified organic etiologies in 15–72% of men with ED, aged below 40 years (6). The reasons for the percentage differences in men with organic ED were patient population and study criteria. However, it would seem more credible for approximately 15–20% of ED causes to be organic in origin (7). Etiology of ED in young men includes vasculogenic and structural conditions, endocrine disorders, neurogenic conditions, medication side effects, intrapsychic disorders, and relational components (5). Vasculogenic causes are a major pathophysiology in organic ED, and arteriogenic ED makes up 32% of organic ED (8).

ED and cardiovascular diseases (CVD) share common risk factors such as obesity, diabetes mellitus (DM), metabolic syndrome, dyslipidemia, smoking, and lack of exercise (9). Researchers have used CVD risk factors or protective factors to study its relationship with ED, and have confirmed that ED prevalence was positively associated with DM, obesity, hypertension, heart disease, and psychological stress in middle and old aged men (10). Among biochemical markers studied, elevated total cholesterol (TC), uric acid (UA), homocysteine (HCY), etc. were known risk factors and elevated high-density lipoprotein cholesterol (HDL) was a protective factor for ED in middle and old aged men (11-13). The pathogenesis of ED is often multifactorial and while risk factors based on the metabolic profile of older men with ED have been identified, those of young men with ED remain to be elucidated.

The objective of this study is to investigate the association of CVD risk and protective factors in young men with ED through comprehensive serological testing.

We present the following article in accordance with the Materials Design Analysis Reporting (MDAR) reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1056).

Methods

Study population

Sample size was estimated according to a previous study and its odd ratio (OR) value (14), the 3rd Edition of *Sample Size Tables for Clinical Studies* (15), and with a case-to-control ratio of 1:4. A total of 289 cases, aged 20–40 years, complaining with ED who presented at the Department of Andrology in China-Japan friendship hospital from October 2016 to October 2019 were recruited. ED diagnosis was made based on patients' complaints of the persistent inability to attain and/or maintain an erection sufficient to permit satisfactory sexual performance for more than 3 months. Specifically, we asked the patients who complained with ED the following three questions. Question 1: is the libido normal (yes/no). Question 2: is the erection hard enough for penetration during sexual intercourse (yes/no). Question 3: whether the penis flaccidity occurs resulting in inability to maintain erection before ejaculation (yes/no). Meanwhile, erectile function was assessed by an erection hardness score (EHS) tactile tool (consisting of four columnar bodies, whose hardness represents erection hardness score grade 1–4, provided by Pfizer Inc.). The patient judges his erection hardness by touching the hardness of the columns. If the answer of question 1 is yes, the answers of questions 2 and 3 are yes, or the answer of question 2 is no, combined with an EHS 1 and 2 indicate the presence of ED.

Meanwhile, medical history-taking and physical examination were carried out to exclude patients with history of mental disorder, penile malformation, spinal cord or pelvic trauma, and peyronie disease.

A total of 289 participants were included in the ED group for serological testing of lipid profiles including total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL); blood glucose (BG); homocysteine (HCY); liver function including alanine aminotransferase (ALT) and aspartate aminotransferase (AST); and renal function including uric acid (UA) and creatinine (CR) (*Figure 1*).

According to the frequency matching ratio of 1:4, 1,155

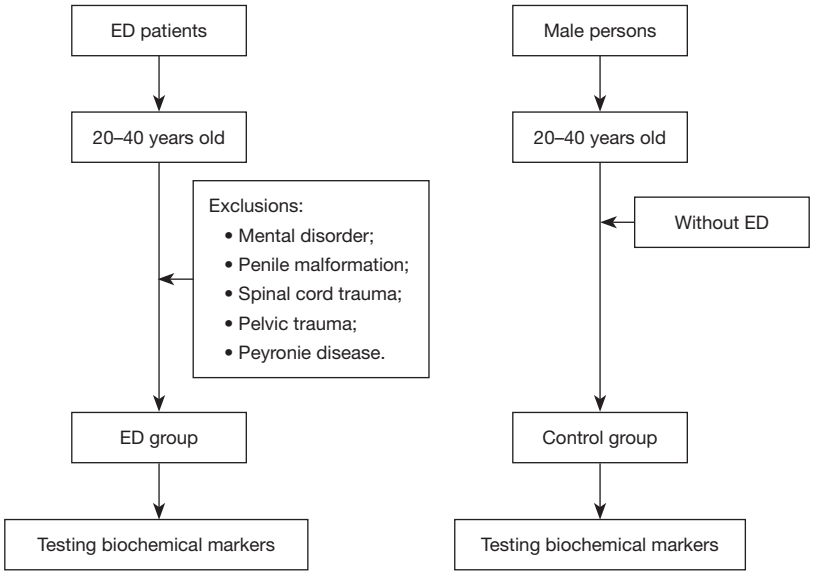

Figure 1 The flow diagram of ED group and control group.

male individuals aged between 20–40 years without ED for physical examinations in our Health Checkup Center of China-Japan Friendship Hospital were recruited as a control group.

In our hospital, male external genitalia examination is part of the routine surgical physical examination. During the male external genital examination, the doctor will ask the participant the following questions. Question 1: have you had sexual intercourse in the past 3 months? (yes/no) Question 2: is the erection hard enough for insertion during sexual intercourse (yes/no). Question 3: whether the penis flaccidity occurs resulting in inability to maintain sexual intercourse before ejaculation (yes/no). If participants are unable to determine whether the erection is normal, erection hardness score (EHS) tactile tool mentioned above can be used as a further assessment tool. If the answers of question 1 and 2 are yes, and the answer of question 3 is no, combined with an EHS 3 and 4 indicate the normal erectile function.

The patients in the control group also have the same exclusion criteria such as mental disorder, penile malformation, spinal cord, or pelvic trauma, and peyronie disease, as patients with ED group. Medical-history taking and physical examination were carried out to exclude the above diseases. Participants in the control group were measured with same biochemical markers test as ED group (*Figure 1*). This study complies with the Declaration of Helsinki (as revised in 2013), and the protocol was approved by Clinical Research Ethics Committee of China-Japan Friendship Hospital (number: 2019-28-k22). All subjects had given their written informed consent prior to the study. The investigation called "The relationship between biochemical markers and erectile function in young cases with erectile dysfunction" was carried out based on a case-control study (ChiCTR1900022840, www.chictr.org.cn).

Measurements

Immediately after the acquisition of venous blood, taken between 08:00–09:00 a.m. after an overnight fast, blood plasma or serum were separated by centrifugation at 3,000×g at 4 ℃ for 15 min. Lipid profiles, BG, HCY, liver function, and renal function were measured in by spectrophotometry (AU-5800, Beckman Coulter Inc., Brea, USA).

Statistical analysis

Continuous variables were expressed as median (interquartile range) when the data were non-normally distributed, and as mean ± SD when normally distributed. For comparisons of continuous variables between the two groups, unpaired Student *t*-test was used for normal distributions, and Mann-Whitney U-test was used for non-normal distributions. ORs in 95% confidence interval (CI) in two groups were computed using binary logistic regression analysis. Receiver operator characteristics (ROC)

analysis was used to evaluate superiority-inferiority of the binary logistic regression model and defined sensitivity and specificity. The area under the ROC curve (AUC) was used as an estimate of model performance, considering that an AUC of 0.5 indicates no ability to definite success of the model. A P value <0.05 for a two-tailed test was considered statistically significant. All statistical analysis was carried out using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Biochemical markers among ED group and control group

This study involved 289 ED patients and 1,155 control subjects, and had no missing data. After comparison, we found no obvious difference for medians of age, TC, TG, HDL, HCY, UA, and ALT in the two groups. Medians of LDL, BG, and CR were much higher, and AST was significantly reduced in the ED group (P<0.01). Statistical data were tabulated with the reference range of our hospital for convenient interpretation of the TC, TG, HDL, LDL, BG, HCY, ALT, AST, UA, and CR results (*Table 1*). LDL-C risk stratification, as per the Guidelines for the prevention and treatment of dyslipidemia in Chinese adults (2016 Revised Revision) (16), were also included in *Table 1*.

ORs, ROC and AUC

To avoid multiple factors influencing the accuracy of results, only biochemical markers of statistical significance in the two groups were included for the binary logistic regression model analysis. The ORs of LDL, BG, AST, and CR to the ED group and control group were 1.279 (95% CI: 1.080–1.515), 1.237 (95% CI: 1.093–1.400), 0.978 (95% CI: 0.963–0.992), and 1.026 (95% CI: 1.015–1.039), respectively (*Table 2*). Through ROC analysis, the cut-off value for binary logistic regression model was 122.675. The area under ROC was 0.608 (95% CI: 0.571–0.644, P<0.001) and the sensitivity and specificity of the model were 43.25% and 72.56%, respectively (*Figure 2*).

Biochemical markers comparison between the younger ED group and older ED group

According to the research "The assessment of vascular risk in men with ED: the role of the cardiologist and general physician" (17), ED patients were subdivided into a younger ED group (20–30 years old) and an older ED group (31–40 years old). There were no significant differences in BG, HCY, ALT, AST, UA, and CR after comparison of the two ED groups. However, the levels of TC, TG, HDL, and LDL yielded significant differences between these two groups (P<0.05) (*Table 3*).

Discussion

The relationship between ED and CVD is relevant in that the risk of CVD should also be evaluated during the evaluation of ED. ED usually precedes CVD onset, and shares common pathophysiological mechanisms with CVD, including endothelial dysfunction, inflammation, and atherosclerosis (18). It is not only strongly predictive of subsequent atherosclerotic CV events, but can also be a sentinel marker of early cardiovascular and other systemic vascular diseases. As a sentinel marker of subsequent atherosclerotic CV events, it is striking when ED presents at a younger age at a younger age (19,20). Therefore, in this study, we focused on men with ED aged 20–40 years.

Erection includes arterial dilation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism (21). It implies that vascular structure plays a crucial role in erection. It is now widely acknowledged that ED can be a consequence of a generalized vascular disorder due to endothelial dysfunction (22). In young ED patients, subclinical endothelial dysfunction is one of the pathological classifications of vascular ED. Young men with no identifiable cause of ED have had evidence of subclinical endothelial dysfunction (5,23).

Elevated LDL is a risk factor of vascular disorders and CVD (16). Previous studies demonstrated elevated LDL was also a risk factor of ED, and increased LDL would lead to aggravated ED (14,24). In these two studies, the patient's age was 42.9±7.9 and 43.56±10.51 years, respectively. In our study, the median age was 28.00 (25.00–29.00) years, thus showing that elevated LDL was a related factor for ED, not only in middle-aged and elderly patients, but also in young men. Increased LDL level can lead to oxidative stress which is associated with endothelial dysfunction (25). In CVD patients, LDL initiates the process of atherosclerotic plaques when it penetrates through dysfunctional endothelium into the walls of arteries (26). In the guidelines for the prevention and treatment of dyslipidemia in Chinese adults (2016 revised version), decreasing LDL to a low level is a well-acknowledged way for the treatment of dyslipidemia (16). The principal role of statins is to reduce LDL levels, which can delay the progress of CVD and reduce its mortality rate. Besides, statins can also improve

Table 1 Biochemical markers between ED and control groups

Biochemical markers	ED group (n=289)	Control group (n=1,155)	Z	P value
Age, years	29.00 (26.50, 32.00)	29.00 (27.00, 34.00)	–1.186	0.236
TC, mmol/L	4.56 (3.96, 5.14)	4.63 (4.05, 5.14)	–0.779	0.436
<5.20	220 (76.12%)	882 (76.36%)		
≥5.20	69 (23.88%)	273 (23.64%)		
TG, mmol/L	1.22 (0.92, 1.84)	1.18 (0.84, 1.81)	1.130	0.259
<1.70	204 (70.59%)	829 (71.77%)		
≥1.70	85 (29.41%)	326 (28.23%)		
HDL, mmol/L	1.11 (0.94, 1.30)	1.13 (0.97, 1.34)	–1.415	0.157
<1.00	95 (32.87%)	328 (28.40%)		
≥1.00	194 (67.13%)	827 (71.60%)		
LDL, mmol/L	2.91 (2.46, 3.38)	2.79 (2.29, 3.28)	2.885	0.004**
≤1.8	7 (2.42%)	78 (6.75%)		
(1.8, 2.6]	86 (29.76%)	396 (34.29%)		
(2.6, 3.4]	128 (44.29%)	444 (38.44%)		
>3.4	68 (23.54%)	237 (20.52%)		
BG, mmol/L	5.39 (5.06, 5.65)	5.25 (4.94, 5.54)	3.524	<0.001**
≤6.11	263 (91.00%)	1079 (93.42%)		
>6.11	26 (9.00%)	76 (6.58%)		
HCY, μmol/L	13.85 (11.27, 19.55)	14.01 (11.80, 19.50)	–1.082	0.279
≤15	172 (59.52%)	678 (58.70%)		
>15	117 (40.48%)	477 (41.30%)		
ALT, IU/L	28.00 (18.00, 42.00)	27.00 (18.00, 43.00)	0.857	0.391
≤40	209 (72.32%)	846 (73.25%)		
>40	80 (27.68%)	309 (26.75%)		
AST, IU/L	20.00 (17.00, 25.00)	21.00 (18.00, 27.00)	–3.319	0.001**
≤42	277 (95.85%)	1,090 (94.37%)		
>42	12 (4.15%)	65 (5.63%)		
UA, μmol/L	393.00 (329.50, 457.00)	389.00 (345.00, 448.00)	–0.066	0.948
≤420	182 (62.98%)	755 (65.37%)		
>420	107 (37.02%)	400 (34.63%)		
CR, μmol/L	78.80 (71.50, 85.65)	75.60 (68.90, 81.90)	4.345	<0.001**
≤106	283 (97.92%)	1154(99.91%)		
>106	6 (2.08%)	1 (0.09%)		

P values for ED group and control group were derived from Mann-Whitney U-test (for continuous dependent variables). *P<0.05, **P<0.01 *vs.* the control group. TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; BG, blood glucose; HCY, homocysteine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UA, uric acid; CR, creatinine.

Table 2 Significant variables after binary logistic regression analysis

Variable	Wald	P value	OR	95% CI
LDL	8.123	0.004	1.279	1.080–1.515
BG	11.398	0.001	1.237	1.093–1.400
AST	8.992	0.003	0.978	0.963–0.992
CR	19.036	<0.001	1.026	1.015–1.039

LDL, low density lipoprotein; BG, blood glucose; AST, aspartate aminotransferase; CR, creatinine; OR, odds ratio; CI, confidence interval.

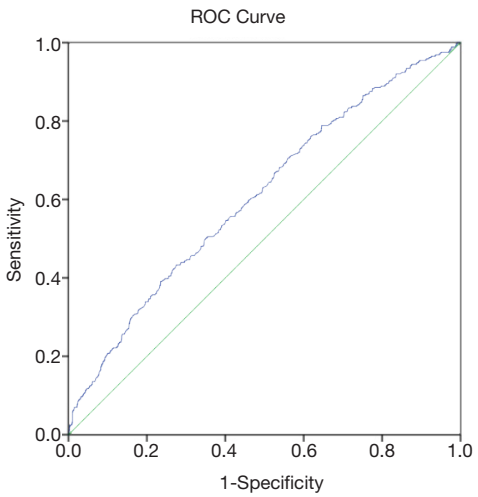

Figure 2 The chart of receiver operator characteristics.

erectile function, as seen in improved international index of erectile function after statin administration (27).

Other studies showed that elevated TC and TG were also risk factors of ED, while elevated HDL was a protective one (11,14,24,28). In the 40–70 years old population, the prevalence of ED as well as the proportion of moderate and severe ED has been known to increase gradually with age (29). However, little is known about the situation of ED population aged 20–40 years. Hence, in this study, the ED group was further divided into two age groups: 20–30 years old and 31–40 years old (17). We then attempted to find the differences between these two groups by comparing biochemical markers. Results showed that the levels of TC and TG were higher, and HDL was lower in the older ED group, compared with those in the younger ED

Table 3 Biochemical markers between the younger ED and older ED groups

Biochemical markers	Younger ED group (20–30 years; n=189)	Older ED group (31–40 years; n=100)	Z	P value
Age, years	28.00 (25.00, 29.00)	34.00 (32.00, 37.00)	14.030	<0.001**
TC, mmol/L	4.38(3.85, 5.00)	4.86 (4.48, 5.42)	4.577	<0.001**
TG, mmol/L	1.12 (0.82, 1.66)	1.49 (1.10, 2.30)	4.310	<0.001**
HDL, mmol/L	1.13 (0.96, 1.31)	1.05 (0.91, 1.26)	–2.300	0.021*
LDL, mmol/L	2.75 (2.30, 3.25)	3.10 (2.75, 3.61)	4.118	<0.001**
BG, mmol/L	5.32 (5.07, 5.64)	5.41 (5.02, 5.71)	0.539	0.590
HCY, μmol/L	13.87 (11.12, 20.01)	13.69 (11.38, 19.02)	–0.319	0.750
ALT, IU/L	27.00 (18.00, 43.50)	29.00 (19.00, 40.75)	0.876	0.381
AST, IU/L	20.00 (17.00, 24.00)	20.00 (17.00, 25.00)	0.163	0.870
UA, μmol/L	392.00 (332.00, 455.00)	394.64±89.20	–0.380	0.704
CR, μmol/L	77.60 (70.90, 85.65)	79.55 (71.78, 85.98)	0.590	0.555

P values for younger group and older group were derived from Mann-Whitney U-test (for continuous dependent variables). *P<0.05, **P<0.01. TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; BG, blood glucose; HCY, homocysteine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UA, uric acid; CR, creatinine; ED, erectile dysfunction.

group. High levels of TC and TG, and decreased HDL may result in endothelial dysfunction causing ED (30). Therefore, hyperlipidemia may play a crucial role in young men with ED.

DM is also a risk factor of ED (31). DM is a group of metabolic diseases characterized by hyperglycemia (high BG) resulting from defects in insulin secretion, insulin action, or both (32). In our study, elevated BG was a related factor in young men with ED (*Table 2*), indicating that BG should be monitored in young men with ED. To better understand the relationship between ED caused by DM and CVD, one animal study showed that in diabetic rats, vascular injury frequently occurred in penile vascular bed prior to other vascular beds, and endothelial dysfunction caused by oxidative stress was first evident in the penis (33). This study provided us an explanation from the molecular level that ED, particularly in DM, precedes systemic CVD. In CVD, elevated BG can lead to endothelial dysfunction by impeding nitric oxide synthesis, increasing the free radical levels, and deteriorating the antioxidant defense mechanisms (34). In addition, vascular smooth muscle cells proliferation and chronic inflammation were also involved in elevated BG towards endothelial dysfunction (35).

Elevated BG alone seems insufficient in accelerating atherosclerosis. However, in presence of extremely high plasma lipid levels, the effect of hyperglycemia appears to accelerate atherosclerosis (36). LDL, either oxidized and/or glycated, were found present in the plasma and affected vasculatures of diabetic patients (37,38). In DM, hyperglycemia induces modification of plasma and tissue proteins by non-enzymatic glycation, a gradual process that culminates with the formation of irreversible advanced glycation end-products (AGE). Irreversibly glycated LDL (AGE-LDL) acts on endothelial cells and results in gradual formation of atheroma in vessel walls, thus exerting proatherogenic effects (39).

Furthermore, clinical observations have found that ED is common in male patients with nonalcoholic fatty liver disease (NAFLD), which easily leads to elevated liver enzymes (40,41). Liver diseases such as cirrhosis and chronic hepatitis, regardless of disease staging, were independent predictors of ED (42).

The levels of serum ALT and AST are independently positively associated with the risk and severity of premature CVD (43). Elevated liver enzymes are associated with indicators of oxidative stress and inflammation, such as C-reactive protein (CRP) (44), of which both are critical in the process of atherosclerosis (45). Increased ALT levels are also associated with endothelial dysfunction and impaired conduit vessel vascular function (46).

In our study, the levels of LDL and BG in the ED group were higher than those of control group, and were identified as related factors of ED. LDL and BG both participate in the pathogenesis of NAFLD and cause disease aggravation (47). Elevated LDL and BG are also responsible for CVD and vascular injuries. Based on the results of LDL and BG, elevated AST should have been a related factor of ED, but in our study, we found that the OR value of ALT was lower than 1. There was no difference in ALT level between the ED and control groups. Correlations of serum AST with liver fat content was weaker than those of ALT (48). Till date, the relationship between AST and ED has not been reported. Our research primarily showed the relationship between AST and ED. The AST value of the ED group was lower than that of the control group, and the OR value of AST was 0.978, indicating that elevated AST might be a related factor of ED in young men. The reason for this has not been clarified, especially in vasculogenic ED. Therefore, a rigorous study on the relationship between AST and ED should be conducted.

In chronic renal failure (CRF) patients, the serum Cr value of those with ED was higher than those without ED (49). The result of our study was consistent with above study. In a retrospective cohort study of 12,493 patients with a small CR increase (1.2–1.5 fold changes compared with admission value) after 26.7±10.6 months follow-up visit, the association of CR changes and the prevalence of CVD was investigated. The study showed that a small CR increase was associated with chronic heart failure, chronic ischemic heart disease, and long-term mortality (50). Therefore, cardiologist and general physician should pay attention to indicators such as serum creatinine, estimated glomerular filtration rate (eGFR), and the ratio of albumin to creatinine in ED patients (17). Our study shows elevated CR is a related factor in young men with ED, and CR should be evaluated among those affected people.

Elevated UA and HCY have previously been considered risk factors of ED and CVD (12,13,51,52). Hyperuricemia or hyperhomocysteinemia can induce endothelial dysfunction and NO reduction (53,54). The levels of UA and HCY have been known to increase with age (55,56). In our study, there was no statistical difference in UA or HCY level between the ED and control groups, indicating that neither elevated UA nor HCY was correlated with ED in young men.

The ROC model was established using the binary logistic regression analysis based on the levels of LDL, BG, CR, and AST. The area under ROC was 0.608 (95% CI: 0.571–0.644,

P<0.001). The sensitivity and specificity of the model were 43.25% and 72.56%, respectively, which indicated that the ability of this model to diagnose ED in young men based on abnormal LDL, BG, CR, and AST levels is weak. However, if the above biochemical markers were normal in young men, then one could possibly relate that the odds of having ED would be lowered, as compared to those with abnormal values.

The causes of ED among young men are multifactorial, including social and physiological factors such as stature, educational level, cigarette smoking, wine drinking, body mass index, lack of exercise, drug (9), which were not investigated in this study. As a result, the ORs values of these indicators and related factors of 20–40 years old young men with ED remains inconclusive. A rigorous design for further investigation is required. Furthermore, men with ED, especially the young adults, are reluctant to be open about their ED issues, which may cause potential bias in the control group.

Conclusions

Elevated levels of LDL, BG, and CR were identified as related factors for ED in young men. Lipid profiles including TC, TG, HDL, and LDL were significantly different between the younger and older age ED groups, which could be selected as potential diagnostic indicators for ED populations aged 20–40 years.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-20-1056). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study complies with the Declaration of Helsinki (as revised in 2013), and the protocol was approved by Clinical Research Ethics Committee of China-Japan Friendship Hospital (number: 2019-28-k22). All subjects had given their written informed consent prior to the study.

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