Interactive effects of intrinsic capacity and obesity on the risk of chronic kidney disease in older patients with type 2 diabetes mellitus

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Abstract

Background: Intrinsic capacity (IC) is a novel concept focusing on normal and healthy aging. The effect of IC on the risk of chronic kidney disease (CKD) in older type 2 diabetes mellitus (T2DM) patients has rarely been studied. We investigated whether a decline in IC is associated with the risk of CKD.

Methods: This is a cross-sectional study. A total of 2482 older subjects with T2DM managed through a disease care program were enrolled. The five domains of IC, namely locomotion, cognition, vitality, sensory, and psychological capacity were assessed. Based on these domains, the IC composite score was calculated. CKD risk was classified according to the KDIGO 2012 CKD definition. Univariate and multivariate analyses were used to assess the association between IC score and CKD risk.

Results: The risk of CKD increased in parallel with IC score (p for trend<0.0001). In multivariate analysis, compared to those with an IC score 0, the odds ratio of having a moderately increased and very high risk stage of CKD was 1.76 (1.31-2.37) times higher for those with an IC score of 2-5. Furthermore, an increased IC score was associated with a higher prevalence of moderate and severe obesity. Moreover, there was a synergistic interaction between IC score and obesity on the risk of CKD (synergy index=1.683; 95% CI: 0.630-3.628), and the proportion of the CKD risk caused by this interaction was 25.6% (attributable proportion of interaction=0.256).

Conclusions: Our findings indicate that IC score may be closely related to the risk of CKD. In addition, there may be a synergistic interaction between IC score and obesity, and this synergistic interaction may increase the risk of CKD.

Background

The older people population worldwide is projected to increase over 1.5 billion within 30 years [1]. The incidence of diabetes mellitus (DM) is also increasing globally, especially in the last few decades with the exponential increase in obesity [2]. Aging is inevitable, and so how to determine, evaluate and maintain healthy, active and successful aging has become an important issue, both for individuals and social-economic systems [3].

Renal impairment always develops in later life in patients with DM, and DM itself is the main cause of chronic kidney disease (CKD). More than 40% of diabetic patients will develop diabetic kidney disease despite controlling serum glucose status and other risk factors such as blood pressure and metabolic syndrome [4, 5]. In the past decades, many studies focused on the determination and early prediction of CKD progression in diabetic patients. A review article published in 2021 reported that numerous risk factors were associated with CKD progression, and grouped them into six categories: sociodemographic and economic, behavioral, genetic, cardiovascular, metabolic, and several novel acute kidney injury biomarkers [6]. Recent advances in molecular biology have led to the identification and establishment of many promising biomarkers for CKD diagnosis and progression, however few have been implemented into routine clinical practice [7]. This is because the prevention of DM-related CKD is very complex,

especially in older patients, and involves many psychological, cognitive and behavioral aspects in addition to the use of medications to control blood pressure and glucose level [8-10].

Intrinsic capacity (IC) was introduced by the World Health Organization in the

2015 World report on aging and health. In the report, the concept of IC was defined as a composite of an individual mental and physical capacities and their interactions with relevant environmental characteristics [11]. IC has been used to measure the capacities of multiple human biological and physiological systems based on body and physical function [12]. In addition, with trajectory over time, IC may provide contextualized monitoring measurements at individual and population levels, which could then be used to inform clinical and public health policy on related individual or population health problems [13]. Recent studies on IC have mainly focused on the evaluation and prediction of the health condition of older populations or aging-related diseases, such as dementia [14, 15]. Only a few reports have used IC in the assessment of other clinical diseases. As impaired renal function always develops in older patients, especially in those with DM, the aim of this study was to evaluate the interactive effect of IC score and obesity on the risk of CKD among 2482 diabetic patients older than 65 years of age. To the best of our knowledge, this is the first study to apply the concept of IC to the risk of CKD in older DM patients.

Materials And Methods

Study design and participants

Totally eight diabetes-specific local clinics in Southern Taiwan and the diabetic department of Kaohsiung E-Da Hospital, Taiwan jointed in this cross-sectional study. A Total of 2482 older outpatient subjects with T2DM were enrolled. The inclusion criteria aged ≥65 years, clinically diagnosed with T2DM between January 2006 and October 2021, relatively healthy without acute illness and without evidence suggesting the possibility of a non-diabetic renal disease (included primary glomerular diseases, drug-induced nephropathy, reflux nephropathy, nephrolithiasis, polycystic kidney and renal-related infectious diseases). The exclusion criteria were patients: 1) aged <65 years; 2) with type 1 diabetes; 3) with history with cancer, liver or urologic diseases; 4) who had been hospitalized for any reasons within 3 months prior to enrollment; 5) with recently use of allopurinol or uricosuric agents for gouty arthritis; 6) who underwent contrast examinations during the follow-up period; and 7) who could not provide complete demographics and personal medical informatio. In addition, to avoid the potential development/presence of primary glomerular diseases, we also excluded patients with persistent hematuria with and without urinary casts.

The diagnosis of T2DM was based on the World Health Organization criteria [16]. All of the patients were followed up in accordance with the diabetes comprehensive management program suggested by the Taiwan National Health Insurance at 3-month intervals. On each follow up visiting, standardized physical examinations, biochemical measurements after fasting, measurements of urine albumin and creatinine were performed. All participants received standard treatment based on recent updated diabetes, hypertension, and dyslipidemia management guidelines. Our study protocol and procedures has been

approved by E-Da Hospital Institutional Review Board with certificate number EMRP-108-111 and EMRP-109-109 and the Ethics Committees of Pingtung Christian Hospital with an approval certificate on 16 December 2005.

Key measures

IC was determined using the ICOPE (WHO) screening tools, including six functional assessments of the following five domains: locomotion, cognition, vitality, sensory (visual and sensory), and psychological symptoms [17]. If subject was unable to complete five chair rises within 14 seconds, limited locomotion mobility was defined. If the patients gave an inappropriate answer to either of two questions on orientation in time and space, or could not recall the three words they were asked to remember , impaired cognitive dysfunction was defined. If subject suffered from weight loss greater than 3 kg over 3 months or with the loss of appetite, malnutrition was defined. If subject had any eye problems such as difficulty in seeing far, reading, eye diseases, or current ophthalmic medical treatment, a visual impairment was defined. If subject failed to hear whispers in the whisper test, a hearing loss was defined. If subject bothered by feeling down, feeling depressed or hopeless, or having little interest or pleasure in doing things over the previous 2 weeks, a depressive symptoms were suggested. Finally, impairment in each item was scored as one point, and IC score was defined as the sum of the six functional assessments, with a higher score indicating greater functional impairment.

Obesity was defined according to the Ministry of Health and Welfare, Taiwan,

criteria instead of the WHO criteria, as it has been suggested that the WHO body mass index (BMI) cut-off point for obesity (≥30 kg/m^2) may be too high for Asians, thereby underestimating associated health risks [18, 19]. Accordingly, we defined underweight as BMI below 18.5 kg/m^2, normal weight as between 18.5≤ BMI <24 kg/m^2, overweight as 24≤ BMI <27 kg/m^2, mild obesity as 27≤ BMI <30 kg/m^2, moderate obesity as 30≤ BMI <35 kg/m^2, and severe obesity as BMI greater than 35 kg/m^2 [20].

Renal function (estimated glomerular filtration rate (eGFR)) was estimated using the CKD-EPI two-concentration race equation [21]: GFR = $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black], where S_{cr} is serum creatinine (mg/dL), κ is 0.7 if females and 0.9 if males, α is -0.329 if females and -0.411 if males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1. Albuminuria was defined by the albumin-to-creatinine ratio (UACR) from spot urine. The presence of albuminuria was defined by at least two measurements of UACR >30 mg/g in a 6-month period during follow-up. The CKD risk estimation using the combination of eGFR and albuminuria categories which suggested by the KDIGO 2012 guidelines was used in our study : low risk (eGFR ≥60 mL/min/1.73 m^2 and UACR <30 mg/g), moderately increased risk (eGFR >60 mL/min/1.73 m^2 and 30< UACR <300 mg/g, or 45< eGFR <60 mL/min/1.73 m^2 and 30< UACR <300 mg/g), high risk (30< eGFR <60 mL/min/1.73 m^2 and UACR >300 mg/g, or eGFR >60 mL/min/1.73 m^2 and UACR >300 mg/g), and very

high risk (15< eGFR <60 mL/min/1.73 m^2 and UACR >300 mg/g, or eGFR <15 mL/min/1.73 m^2 and UACR >300 mg/g) [22].

Laboratory measurements

Routine tests including a clinical examination, recent medication side effect assessment, body weight, blood pressure, urinary sediment and urinalysis, complete blood count, serum chemistry, and HbA1c concentrations were performed during each regular visits. The urinary albumin concentration was measured after overnight fasting by immunoturbidimetry (Beckman Instruments, Galway, Ireland). The detection limit was 2 mg/L, with the interassay and intraassay coefficients of variance <8%. In the study admission, the patients were defined as normoalbuminuric if they had a UACR <30 mg/g in at least two consecutive overnight urine collections. If the patient had first UACR measurement >30 mg/g, a repeat urine test will be asked and checked to confirm the diagnosis of albuminuria within 3 to 6 months in the follow-up period later. If the urine specimen showed the presence of urinary infections, the specimen will not be used and a new sample was collected after antibiotics treatment. To exclude primary renal diseases, abnormal urinary sediment should not be noted in the urine specimen (presence of any protein, red blood cells, hemoglobin, white blood cells, nitrites or casts). Serum creatinine was measured by the Jaffe method. Serum HbA1C, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, hemoglobin, creatinine, and glucose were determined using a parallel-multichannel analyzer (Hitachi 7170A, Tokyo, Japan) by standard commercial methods after an overnight fast as in our previous report [23].

Variables

All participants completed a standard questionnaire that assessed age, gender, cigarette use, history of disease (T2DM, diabetes duration, hyperlipidemia, hypertension, heart disease, and cancer) in face-to-face interviews with trained interviewers. Subject's blood pressure was measured by trained clinical assistants with digital automatic blood pressure monitor (model HEM-907; Omron, Omron, Japan) after resting for 5 minutes. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg, a diastolic blood pressure (DBP) ≥90 mmHg, or if the patient was recent using antihypertensive medication. Anthropometric parameters including BMI (kg/m^2) were measured. Hyperlipidemia was defined according to the ATP III criteria as following: triglycerides ≥150 mg/dl, and/or HDL-C <35 mg/dl in men or <39 mg/dl in women, and/or total cholesterol ≥200 mg/dl, and/or LDL-C ≥130 mg/dl, or those undergoing treatment for lipid disorders.

Statistical analysis

Data normality was analyzed using the Kolmogorov-Smirnov test. Continuous, normally distributed variables are presented as mean ± SD, and non-normally distributed variables as median (interquartile range). Categorical variables are presented as frequencies and/or percentages. Baseline characteristics were compared between groups using one-way analysis of variance (ANOVA) for normally distributed variables. The chi-square test was used to compare categorical variables.

Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of CKD in each IC score, compared with an IC score of 0 as the reference. To test linear risk trends, a tertiles as a continuous variable in the regression models was used. Biochemical parameters according to IC score at baseline were tested for trends.

ORs and corresponding 95% CIs were calculated using univariate and multivariate logistic regression models to evaluate the relationships between IC scores and the risk of CKD. A p value <0.05 was considered to be statistically significant. JMP version 7.0 for Windows (SAS Institute, Cary, NC, USA) was used in our analysis.

An Excel sheet provided by Andersson and co-authors [24] was used into the database and compute the relevant indicators of interactions. Using a logistic regression model, a value was obtained and taken as the estimated additive interaction between IC score and obesity status. The interaction based on the additive model was determined using the following indexes: the relative excess risk of interaction (RERI), attributable proportion of interaction (API), synergy index (SI), measure of multiplicative interaction for risk ratios [25] and their 95% CIs using the delta method [26]. The RERI refers to the excess risk due to the interaction relative to the risk without exposure. The API is the attributable proportion of disease caused by the interaction in subjects with both exposures. The SI refers to the excess risk from both exposures when there is a biological interaction due to the risk from both exposures without interaction. The RERI has been showed to be the best measure of interaction using a proportional hazards model [27]. If the RERI and AP are equal to 0, absence of additive interactions was defined [28]. Finally, an indicative biological interaction is considered when RERI >0, AP >0, S >1, or a measure of multiplicative interaction for risk ratios >1.

Results

Characteristics of the participants

A total of 2482 patients with T2DM aged 65-99 years were included, and their baseline characteristics and clinical data are presented in Table 1. The mean ± SD age was 72.4 ± 5.8 years and known duration of diabetes was 13.5 ± 9.0 years. The prevalence rates of hypertension, hyperlipidemia, and smoking were 62.5%, 78.8%, and 15.6%, respectively. The patient's mean eGFR was 68.9 ± 22.0 mL/min/1.73 m^2, and the median (interquartile range) UACR was 19.2 mg/g (9.7-54.3 mg/g).

Main characteristics according to IC score

The general characteristics of the 2482 patients grouped according to IC scores are reported in Table 2. The numbers of patients with an IC score of 0, 1, and 2-5 were 1525 (61.4%), 655 (26.4%), and 302 (12.2%), respectively. The patients with an IC score 2-5 were more predominantly female, had severe obesity, high risk and very high risk of CKD stage, higher rates of both insulin and oral hypoglycemic

agents, older age, and longer diabetes duration than those with an IC score of 0 or 1. Furthermore, the patients with an IC score 2-5 had a higher prevalence of hypertension, moderate obesity, severe CKD risk, and higher rate of treatment with angiotensin receptor blockers than those with an IC score of 0. There were no significant differences in hyperlipidemia, current smoker, waist-to-hip ratio, SBP, DBP, and statin treatment among the three groups.

Association between IC score and CKD risk

We investigated associations between IC score and CKD risk (Table 3). The moderately increased risk and very high risk stages of CKD increased in parallel with IC score. Accordingly, there were increases in the ORs for the association with moderately increased risk and very high risk stages of CKD relative to an IC score of 0, OR=1.0; score 1, OR=1.36; score 2-5, OR=2.57 (p for trend across increasing IC scores <0.0001).

Biochemical characteristics according to IC score

Biochemical characteristics stratified by IC scores revealed that HbA1c, fasting glucose, BMI, eGFR, creatinine, and hemoglobin levels were significantly associated with IC scores (p for trend <0.05, Table 4).

Association of IC score with a moderately increased risk and very high risk stage of CKD

We used univariate and multivariate logistic regression models to investigate associations between IC score and CKD risk (Table 5). Patients with an IC score of 1 had an increased risk of CKD compared with those who had an IC score of 0 in model 1 and model 2. However, those with an IC score of 1 did not have an increased risk of CKD compared with those who had an IC score of 0 in model 3. Patients with an IC score of 2-5 had a higher risk of moderately increased risk and very high risk stages of CKD compared with those with an IC score 0 in model 1, model 2, and model 3 (OR: 2.57, 95% CI: 1.97-3.36, p<0.0001, OR:1.82, 95% CI: 1.38-2.42, p<0.0001, and OR: 1.76, 95% CI: 1.31-2.37, p=0.0002, respectively).

Joint impacts of IC score and obesity on the risk of CKD

Because an increased IC score was associated with higher moderate and severe obesity, we investigated the additive interaction effect of IC score and moderate and severe obesity on the risk of moderately increased risk and very high risk stages of CKD, including IC score 0 and normal weight, IC score 0 and moderate and severe obesity, IC score 1-5 and normal weight, and IC score 1-5 and moderate and severe obesity. In univariate analysis, the patients with an IC score 0 and moderate and severe obesity had a 1.90-fold higher risk (OR=1.90; 95% CI: 1.35-2.69, p=0.0003) than those without. In addition, the patients with an IC score 1-5 and normal weight had a 1.69-fold higher risk (OR=1.69; 95% CI: 1.29-2.23, p=0.0002) than those without. Moreover, the patients with an IC score 1-5 and moderate and severe obesity had a 3.12-fold higher risk (OR=3.12; 95% CI: 2.14-4.60, p<0.0001) than those without (data not shown). In multivariate analysis, the patients with an IC score 0 and moderate and severe obesity had a 1.64-fold higher risk (OR=1.64; 95% CI: 1.12-2.39, p=0.011) than those without. Furthermore, the patients with an IC score 1-5 and normal weight had a 1.38-fold higher risk (OR=1.38; 95% CI: 1.03-1.86, p=0.034) than those

without. Moreover, the patients with an IC score 1-5 and moderate and severe obesity had a 2.71-fold higher risk (OR=2.71; 95% CI: 1.82-4.10, p<0.0001) than those without (Figure 1). The RERI, API, SI, and measure of multiplicative interaction for risk ratios were 0.695, 0.256, 1.683, and 1.200, respectively. The RERI >0, API >0, SI >1, or a measure of multiplicative interaction for risk ratios >1 suggested that there may be a synergistic interaction between IC score 1-5 and moderate and severe obesity on the risk of moderately increased risk and very high risk stage of CKD. In addition, the API was 0.256 after adjusting for all confounders, indicating that the proportion of risk of moderately increased risk and very high risk stage of CKD that may have been caused by the interaction of IC score 1-5 and moderate and severe obesity was 25.6% in the patents with a moderately increased risk and very high risk stage of CKD.

Discussion

In this study, we found that IC score was related to and had a synergistic interaction with obesity on the risk of CKD in diabetic patients aged ≥65 years. IC is a novel concept of healthy aging introduced by the WHO to help develop public health strategies in response to the aging population, as adults older than 60 years are expected to account for 12% to 22% of the global population (approximately 2 billion people) by 2050 (https://www.who.int/news-room/fact-sheets/detail/ageing-and-health). Most recent studies using IC score have focused on frailty, physical resilience and dementia, and rarely on other chronic diseases [17,29]. Older populations have more comorbidities, which may impair renal function. In this study, we found that the IC score was very sensitive, as even a score of 1 was associated with an increased risk of CKD, and this association persistent after adjustments using logistic regression analysis (Table 5).

We found that IC score was associated with age, female sex, hypertension and obesity status, and a higher IC impairment score was associated with higher BMI, and the use of insulin and angiotensin receptor blockers. Mean Hba1c, fasting blood glucose, BMI, and UACR levels were significantly positively associated with IC score, whereas mean eGFR and hemoglobin levels were negatively associated with IC score (Tables 3 and 4). Associations between IC score with demographic characteristics and metabolic control profiles have seldom been described, although a recent study reported that dyslipidemia and not hypertension status was associated with IC score [30, 31]. Most previous studies on IC have focused on interactions among chronic diseases, self-care capacity and social engagement, but not on disease progression or organ function. Two studies reported that impaired IC may be related to renal function and elevated heart failure markers [15, 32], and two other studies reported that impaired renal function was associated impaired mobility and poor nutrition [31, 33]. Therefore, it is important and reasonable to investigate and clarify the associations and interactions between IC score and the risk of renal function impairment, demographic characteristics and metabolic control profiles. The detailed pathogenetic mechanisms between IC and metabolic derangement are discussed below.

The most important finding of this study is the synergistic interaction of IC score and obesity on the risk of CKD after analyzing multiple interactions for risk ratios (Figure 1). Several recent studies have reported that obesity is associated with older age and increased rates of frailty and mobility, and that this impairs the patient's quality of life [34]. In 2000, Baumgartner termed the phrase sarcopenic obesity [35],

and it has been shown to be especially prevalent and associated with many adverse health conditions in older adults [36]. Sarcopenic obesity is defined as the combination of obesity with low muscle mass and strength [35]. Although it can be caused by age-related changes in body composition [37], several pathways have also been proposed, including a sedentary lifestyle with less physically activity [38], higher inflammation status [39], insulin resistance [40], lower growth hormone and testosterone levels [41, 42], relative malnutrition [43], and poor psychological status [44], all of which occur in older patients.

In a literature review, sarcopenic obesity was associated with frailty among older adults [45], and with the risk of coronary artery disease and all-cause mortality [46, 47]. Recent studies have further shown an association between sarcopenic obesity and chronic renal disease, especially in those with diabetes-related renal impairment [48]. This may explain why insulin resistance, the over-expression of adipokines, and inflammation processes have been associated with obesity and CKD progression [49-53]. Taken together with frailty, it is reasonable that all of these adverse conditions could impair IC and aggravate the deterioration in renal function. Our study provides further information to support that obesity with pre-frailty is associated with the pathogenesis of CKD.

The interactions among muscle wasting, obesity and diabetic nephropathy are unclear. Advanced glycosylated end products (AGEs) have been associated with hyperglycemia, muscle wasting, and impaired renal function in vivo and in vitro [54], In addition, insulin resistance, oxidative stress, inflammation, uremic toxin toxicity, metabolic acidosis, vitamin D deficiency and protein energy wasting occur in patients with diabetic nephropathy, and they also result in muscle loss and abnormal fat deposition in CKD patients [48]. Taken together, these findings show that it is important to detect and evaluate sarcopenic obesity to allow for the more intensive management of diabetes and renal dysfunction in older patients.

Most of the current strategies to prevent the complications of diabetic nephropathy still focus on preventing hyperglycemia, the early diagnosis of kidney disease, and antihypertensive treatment to reduce renin-angiotensin system activity [48]. To reduce complications and disability directly or indirectly caused by diabetes, the American Diabetes Association has also launched numerous projects, such as the Diabetes Self-Management Education and Support (DSMES) and ADCES7 Self-Care Behaviors™ to help clinical physician and patients to monitor clinical, psychosocial and behavioral aspects of diabetes [55, 56]. However, none of these focus on the evaluation or detection of sarcopenic obesity-related CKD in diabetic patients.

Rapid and accessible assessment tools to evaluate the health and physical condition of older adults are needed, as not everyone can access medical facilities or afford the cost of biochemical and imaging examinations. Healthy aging is a process of developing and maintaining functional ability that enables well-being in old age. IC considers both physical and mental abilities by determining the functional ability combined with environmental factors and their interaction (https://apps.who.int/iris/handle/10665/186463), and it has been proven that using IC is more effective to assess older populations than focusing on specific diseases or biomarkers [15]. In this study, we applied the IC

concept to older diabetic patients, and found that impaired IC combined with obesity could further screen out patients at high risk of CKD even before changes in UCAR, eGFR and creatine levels, which are used to evaluate renal function and early CKD clinically.

There are still some limitations to this study. First, we lacked data on inflammation, adipocytokines and other specific kidney injury markers, and further investigations are warranted to investigate their association with IC and CKD progression. Second, due to case number limitation, although the impairment of IC with even an IC score of 1 showing a significant association with CKD risk, further evaluations are needed to clarify which components of IC impairment have the strongest effects. The current observation is a preliminary cross-sectional association study, and further investigations are needed to examine the long-term predictive ability of IC score on the progression of CKD.

Conclusions

This is the first study to show that IC impairment was associated with the risk of CKD,and that obesity status further interacted and synergistically increased the risk of CKD among older diabetic patients. Earlier interventions for IC impairment and obesity should be performed in this population to help prevent CKD.

Abbreviations

DM: Diabetes mellitus; CKD: Chronic kidney disease; IC: Intrinsic capacity; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; eGFR: Estimated glomerular filtration rate; UACR: Urinary albumin-to-creatinine ratio; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ANOVA: Analysis of variance; ORs: Odds ratios; Cis: Confidence intervals; RERI: Relative excess risk of interaction; API: Attributable proportion of interaction; SI: Synergy index; AGEs: Advanced glycosylated end products; DSMES: Diabetes Self-Management Education and Support.

Declarations

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Author Contributions

Conceptualization, W.-H.T. and Y.-J.L.; Data curation, Y.-J.L.; Formal analysis, W.-H.T. and Y.-J.L.; Funding acquisition, T.-H. Y.; Investigation, W.-H.T., T.-H. Y., and Y.-J.L.; Methodology, W.-H.T. and Y.-J.L.; Writing-original draft, W.-H.T., T.-H. Y., H.-L. L., and Y.-J.L.; Writing-review and editing, W.-H.T., T.-H. Y., H.-L. L., and Y.-J.L. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committees of Pingtung Christian Hospital and E-Da Hospital with a Clinical Trial Approval Certificate from Pingtung Christian Hospital on 16th December 2005 and E-Da Hospital Institutional Review Board number EMRP-108-111 and EMRP-109-109. All experiments were carried out in accordance with the approved guidelines. Written informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interest to report.

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Tables

Table 1. Baseline characteristics of the study population

Characteristic	Total (N = 2482)
Age (years)	72.4 ± 5.8
Female (n, %)	1374 (55.4)
Known diabetes duration (years)	13.5 ± 9.0
Hypertension (n, %)	1552 (62.5)
Hyperlipidemia (n, %)	1956 (78.8)
Smoker (n, %)	359 (15.6)
Estimated glomerular filtration rate (ml/min/1.73 m^2)	68.9 ± 22.0
Body mass index (kg/m^2)	25.6 ± 4.0
Urinary albumin/creatinine ratio (mg/g)	19.2 (9.7-54.3)
Creatinine (µmol/L)	97.2 ± 53.0
Body mass index (kg/m^2)	25.6 ± 4.0
Systolic blood pressure (mmHg)	129 ± 16
Diastolic blood pressure (mmHg)	73 ± 11
Total cholesterol (mmol/L)	4.1 ± 0.8
Triglycerides (mmol/L)	1.3± 0.7
High-density lipoprotein-cholesterol (mmol/L)	1.4 ± 0.4
Low-density lipoprotein-cholesterol (mmol/L)	2.1 ± 0.6
Fasting glucose (mmol/L)	8.5 ± 3.4
HbA1c (%)	7.3 ± 1.2
Statins (n, %)	1919(77.3)
Angiotensin receptor blocker (n, %)	1085 (43.7)
Type of treatment (%)	
(OHA/Insulin/Both)	67.8/3.2/29.1

Data are expressed as the mean ± SD, number (percentage), or median (interquartile range).

Table 2. Main characteristics according to intrinsic capacity score

	IC score 0	IC score 1	IC score ≥2	p value
Number	1525	655	302	
Age (years)	71.2±5.0	73.2±5.9	77.0±6.6	<0.0001
Sex, female (n, %)	790(51.8)	393(60.0)	191(63.3)	<0.0001
Diabetes duration (years)	13.1±8.8	13.7±9.2	15.2±9.2	0.001
Hypertension (n, %)	917(60.1)	438(66.9)	197(65.2)	0.007
Hyperlipidemia (n, %)	1217(79.8)	503(76.8)	236(78.2)	0.276
Current smoker (n, %)	315(20.7)	121(18.5)	50(16.6)	0.184
Waist-to-hip ratio	0.92±0.07	0.93±0.07	0.93±0.07	0.156
Systolic blood pressure (mmHg)	128±15	130±16	130±19	0.076
Diastolic blood pressure (mmHg)	73±11	73±11	73±11	0.669
Obesity status (n, %)				
Underweight	19(1.3)	11(1.7)	5(1.7)	0.681
Normal weight	571(37.4)	210(32.1)	105(34.8)	0.052
Overweight	485(31.8)	199(30.4)	98(32.5)	0.752
Mild obesity	278(18.2)	129(19.7)	44(14.6)	0.160
Moderate obesity	147(9.6)	88(13.4)	39(12.9)	0.019
Severe obesity	25(1.6)	18(2.8)	11(3.6)	0.047
Chronic kidney disease risk (n, %)				
Low risk	789(51.7)	289(44.1)	89(29.5)	<0.0001
Moderately risk	379(24.9)	154(23.5)	77(25.5)	0.740
High risk	192(12.6)	108(16.5)	68(22.5)	<0.0001
Very high risk	165(10.8)	104(15.9)	68(22.5)	<0.0001
Type of treatment (%)				
(OHA/Insulin/Both)	71.6/2.1/26.3	65.5/4.6/30.0	53.7/5.3/41.0	<0.0001
Statins (n, %)	1193(78.2)	494(75.4)	232(76.8)	0.348
Angiotensin receptor blocker (n, %)	626(41.1)	317(48.4)	142(47.0)	0.003

Data are presented as mean ± SD or number (percentage). IC, intrinsic capacity; OHA, oral hypoglycemic agents.

Table 3. Odds ratio (ORs) of chronic kidney disease risk stage according to intrinsic capacity score

	Chronic kidney disease risk stage†			
Variables	Moderate risk to very high risk	Low risk	OR (95%CI)	p-value
IC score				
Score 0	736 (48.3%)	789	1.00 (reference)	
Score 1	366 (55.9%)	289	1.36 (1.13-1.63)	0.001
Score ≥2	213 (70.5%)	89	2.57 (1.97-3.36)	<0.0001
p for trend			<0.0001	

IC, intrinsic capacity. †CKD risk stage was defined according to the 2012 KDIGO definition [22]. OR, odds ratio; CI, confidence interval.

Table 4. Biochemical characteristics according to intrinsic capacity score

	IC score 0	IC score 1	IC score ≥2	p for trend
Number	1525	655	302	
Body mass index (kg/m^2)	25.4±3.8	26.0±4.2	25.8±4.2	0.001
HbA1c (%)	7.2±1.1	7.2±1.2	7.5±1.4	0.002
Fasting glucose (mmol/L)	8.4±3.3	8.5±3.4	8.9±3.8	0.012
Total cholesterol (mmol/L)	4.1±0.8	4.1±0.8	4.0±0.8	0.803
Triglycerides (mmol/L)	1.3±0.8	1.3±0.7	1.3±0.6	0.685
HDL cholesterol (mmol/L)	1.4±0.4	1.4±0.4	1.4±0.4	0.892
LDL cholesterol (mmol/L)	2.1±0.6	2.1±0.7	2.1±0.6	0.709
Uric acid (mmol/L)	0.3±0.1	0.3±0.1	0.3±0.1	0.703
eGFR (ml/min/1.73m^2)	77.2±20.5	73.3±21.5	71.0±23.0	<0.0001
UACR (mg/g)	17.1(8.8-46.5)	21.0(10.9-60.9)	29.3(13.4-83.6)	0.077
Creatinine (μmol/L)	94.6±48.6	102.5±67.2	107.9±56.6	<0.0001
Hemoglobin (g/L)	138±17	133±17	131±17	<0.0001

Data are presented as mean ± SD or median (interquartile range). HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate, UACR, urinary albumin-to-creatinine ratio.

Table 5. Logistic regression of the association of intrinsic capacity score with moderately increased risk and very high risk stage of CKD

	Model 1		Model 2		Model 3	
Variables	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
IC score						
0	Ref		Ref		Ref	
1	1.36 (1.13-1.63)	0.001	1.21 (1.00-1.46)	0.049	1.12 (0.92-1.37)	0.271
≥2	2.57 (1.97-3.36)	<0.0001	1.82 (1.38-2.42)	<0.0001	1.76 (1.31-2.37)	0.0002

Figures

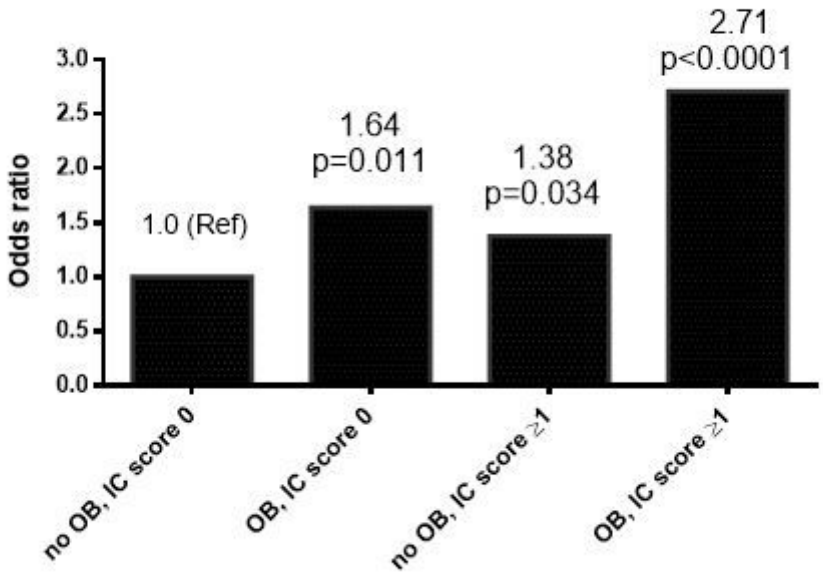

Figure 1

Interaction schematic diagram between moderate and severe obesity (OB) and intrinsic capacity (IC) score on risk of chronic kidney disease after adjusting for multiple confounders.