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Research Article

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Glucose Lowering Treatment Patterns in Type 2 Diabetes Mellitus (T2DM) Management: A Real World Study from the Rural-Urban Fringe Zone of Suzhou City, Jiangsu Province

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Abstract

Objective*:* To manage type 2 diabetes mellitus (T2DM) using glucose lowering regents(GLRs) effectively, the patterns of treatment were studied based on real world data from a rural-urban fringe zone of Suzhou city, Jiangsu Province.

Methods*:* A cross-sectional study was carried out using data from T2DM management as basic public health service during August 2018 to January 2021 in the urban-rural fringe zone in Suzhou city, Jiangsu Province, China. HbA1c and detail information of the diabetic treating histories were collected when registered for T2DM management. HbA1c<7.0% was considered as T2DM controlled (i.e., HbA1c≥7.0% as the uncontrolled), and glucose lowering treatments patterns for medicine and insulin usages were described.

Results*:* Among GLRs in this rural-urban fringe zone, sulfonylurea (SU), metformin (MET) and alpha glucosidase inhibitor (AGI) were the most frequently used oral antidiabetic drugs(OADs), and 12% (150/1207) patients used short-term insulin(STI). More than 60% (764/1207) T2DM patients were managed with regent combinations. SU and MET were the most commonly observed combination for glucose lowering which accounted for 41%(489/1207) of patients under management and three quarters (371/489) were two-drug combinations. SU combined with AGI was observed as the second with proportion of 11% (127/1207).

More regent numbers with less control rates for T2DM management was observed. Single SU with control rate (95% CI) of 51.4% (108/210, 95% CI 44.5%-58.4%), nearly twenty percentage higher than that of then combination therapy (32.9%,189/386, 95% CI 29.0%-36.9%)($\chi 2$=22.526, P<0.001). Among two-combinations of SU+MET, SU+AGI, AGI+MET and STI+MET, HbAc control rates were listed as 33% (95%CI 29%-37%), 35% (95%CI 26%-44%), 28% (95%CI 19%-38%) and 21%(95%CI 11%-33%), respectively.

Using SU as example, combinations had lower levels of HOMA-β scores which meant lower function of islets.

Conclusions*:* Antidiabetic drugs treatment patterns followed the national recommendation in the rural-urban fringe zone, however, the effects were not as expected, i.e., more glucose lowering regents would not raise the controlled rates and recently discovered regents should be included in the future managements.

Keywords: Glucose lowering regents(GLRs), oral antidiabetic drugs, T2DM management, rural-urban fringe zone

Abbreviations

T2DM: type 2 diabetes mellitus; FPG: fasting plasma glucose; 2hPG: 2h postprandial glucose; FPI: fasting plasma insulin; 2hPI: 2h postprandial insulin; HbA1c: glycosylated hemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance; HOMA-β: homeostasis model assessment of beta-cell function; SU: sulfonylurea; AGI: α-glucosidase inhibitor; DPP-4i: dipeptidyl peptidase-4 inhibitor; Non-SU: None sulfonylurea;

GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT2i: sodium-glucose cotransporter-2 inhibitor; TZD: thiazolidinedione; STI: short-term insulin; LTI: long-term insulin; MET,metformin; OADs: oral antidiabetic drugs; GLRs: glucose lowering regents

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease, and controlling hyperglycemia is the goal of its management. Generally, medical nutrition therapies and exercises are the basic measures in T2DM management. However, as the course progresses, diet and exercise often fail to reach the glucose control target. The dependence on glucose lowering regents(GLRs) gradually increases, and timely treatment should be adopted, including hypoglycemic drugs and insulin injections alone or in combinations [1]. Chinese guidelines recommend metformin as the first-line medication for controlling hyperglycemia in T2DM and as the basic medication in drug combinations, while sulfonylurea(SU), none sulfonylurea (Non-SU), α-glycosidase inhibitors (AGI), thiazolidinedione (TZD), dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium-glucose cotransporter-2 inhibitor (SGLT2i), glucagon-like peptide-1 receptor agonist(GLP-1RA) and insulin are the main combination regents. Pharmacological regents alone or combination can be selected based on factors such as hypoglycemic risk, weight, economic conditions, and accessibility. In large urban communities in China, oral antidiabetic drugs(OADs) are the main ways for T2DM management. However, drug selection is different due to disease progress, clinical medication habits or other factors. For example, SUs are the most commonly used OAD among T2DM patients in Shanghai, with a usage rate of 62.4%, far higher than the levels in other cities (40-50%) [2]. In Italy, general practitioners, who play a major role in T2DM management, can only prescribe first-generation antidiabetic drugs, such as MET, SU, glinides, acarbose and glitazones, while the prescription of more recently marketed antidiabetic drugs, such as GLP-1RA, DPP-4i and SGLT2i, is restricted to diabetologist only, based on a therapeutic plan [3]. It can be seen that even under the same guidelines, there are differences in medication patterns.

The availability of new antidiabetic drugs has led to complex treatment patterns and to changes in drug utilization. A unique pattern of prescription is observed amongst Japanese patients with T2DM, i.e., DPP-4i, rather than MET, is predominantly used as the first-line treatments [4,5]. The growing number of people with T2DM has a great impact not only on clinical outcomes, but also on economic burden of the healthcare systems [3]. Therefore, the treatment approach should be substantially different from traditional methods. And, the introduction of new medications has led to inquiries regarding the role of older drugs in diabetes management [6]. Costs associated with diabetes-related complications represent the most relevant part of the national healthcare expenditure for diabetes and are higher than the costs of managing diabetes itself. Thus, an effective therapy with a good metabolic control can reduce the risk of complications and represents a valid strategy from an economic point of view [7].

From 2018, the local government initiated the project of chronic diseases management including T2DM in Suzhou, Jiangsu province. Each community health service center has set a team consisting of two trained-full-time physicians and a trained-full-time nurse in charging the T2DM management. In the management, the first step was T2DM patient registration, then carried out basic information investigations, physical examinations and checkups, thus regularly following-ups were implemented for the management. It is recognized that to treat with a combination therapy from the time of initial diagnosis is the most effective way in T2DM management [6]. So, based on the baselines, especially pharmacological regimens in this area, the treatment patterns for T2DM management would be explored.

Material and Methods

Subjects

From August 2018 to January 2021, the local government initiated the project of chronic diseases management including T2DM. Three health service centers (urban-rural fringe zone) implemented in the T2DM management as the basic public health service, which covers about 20000 residents inhabited near a big

lake (Taihu Lake) with the first class of government economy. These residents diagnosed or had the histories of T2DM were welcomed to participate in the project. After registration, basic information was investigated, physical examinations and checkups were recorded and regularly following-ups were carried out for T2DM management.

Registered T2DM patients met the inclusion criteria: (1) adults aged ≧30 years old diagnosed with diabetes based on fasting plasma glucose (FPG) ≥7.0mmol/L, or 2h plasma glucose (2hPG) during an oral glucose tolerance test ≥11.1mmol/L, or history of T2DM; (2) residents of Suzhou who visited the community health service center regularly; and (4) willing to participate in T2DM management.

Those with T1DM, or T3cDM or any other form of diabetes were excluded for T2DM management. Also data missing, without information of diabetes history or treating histories were excluded.

Biochemical tests

Glycosylated hemoglobin (HbA1c), plasma glucose (FPG and 2hPG) concentrations and insulin levels (FPI and 2hPI) were measured by biochemical tests. HbA1c was measured using high performance liquid chromatography and blood glucose concentrations were measured using the hexokinase method. And insulin levels were measured using chemiluminescent immunoassay method.

Data collection

This paper is a part job of a following-up studies, in this cross-sectional study including T2DM patients registered during August 2018 to January 2021 and a medical staff team was trained for data collection. Self-report basic information and personal habits and individual disease histories and treatments were collected by face to face investigation, physical checkups and laboratory tests were carried out for body indexes, blood and urea results. Especial for the FPG, 2hPG, FPI and 2hPI levels were measured and the history of diabetes and the pharmacological regimens including medicines and insulins were investigated.

Using original data obtained from registration checkups, body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of beta-cell function (HOMA-β) were calculated. In brief, BMI was calculated as ratio of body weight(kg) and height(m)2. HOMA-IR index values were gotten as the FPG(mmol/L)×FPI(μU/mL)/22.5. HOMA-β index values were calculated as 20 × FPI (μU/mL)/(FPG (mmol/L) –3.5).

All participants were informed that the data may be used for scientific researches and a signed consent form was obtained. The study was conducted in accordance with the declaration of Helsinki and approved by Clinical Research Ethics Committee of The Affiliated Suzhou Hospital of Nanjing University Medical School.

The controlled T2DM

All the criteria in this study referred to the guidelines for risk factors and control standards for prevention and treatment of T2DM in China (2020 Edition) [1]. In brief, the glycemic control of T2DM was plasma HbA1c < 7.0% and named as the controlled, on the contrary, plasma HbA1c ≥7.0% named as the uncontrolled.

Data processing and statistical methods

Data were first checked and then decrypted for the sake of personal confidentiality before analysis. After establishing the database, data were cleaned for unqualified data before analysis. The distribution of continuous data was checked first and then original data was used for calculation for normal distribution, and data were squared or logarithm transformed for skew distribution if condition permitted (Supplement. Fig. 1). In detail, disease duration of T2DM, HbA1c and C peptide were transformed using squared method. FPG, FPI, 2hPI, HOMA-IR and HOMA-β were transformed using ln logarithm method. Quantitative data were presented using mean ± standard deviation or mean ± standard error or median with quartile percentiles. Student t-test (or t'-test) was used for the comparison between groups. Qualitative data (or counting data) were described as percentages or proportions, and comparisons between groups were carried out using chi-square test. $P < 0.05$ was considered as statistically significant of two sides.

Considering the fact that duration of T2DM may influence the HOMA-β, HOMA-IR and C-peptide, thus an analysis of covariance (ANCOVA) model with T2DM duration as covariates and least-squares means were calculated for these indexes. The research data analysis and processing were completed by professional statistical analysts using SPSS software version 26.00 (Armonk, NY: IBM Corp).

The analysis process of the subjects was shown in Fig. 1.

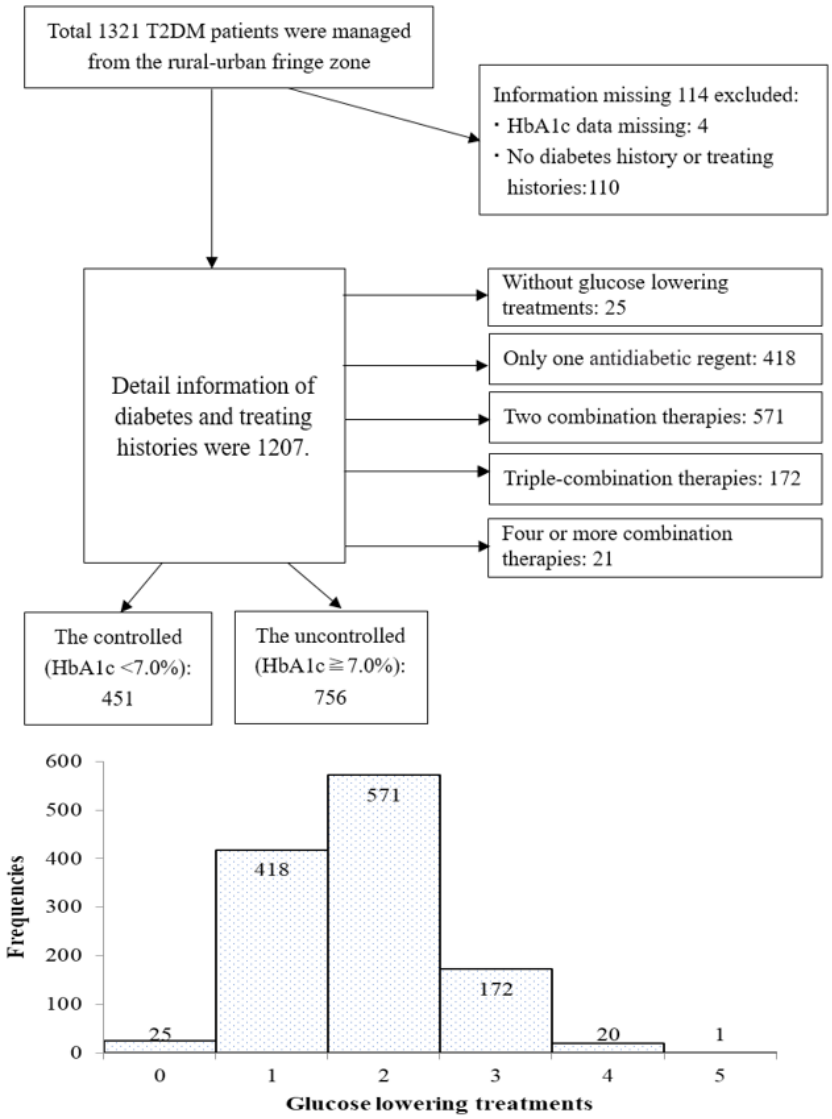

Figure 1: *Data process flow for investigating the control of T2DM in a rural-urban fringe zone in Suzhou city, Jiangsu Province, China.*

Results

As a long-term management of T2DM in the rural-urban fringe zone located in Suzhou city, Jiangsu province, this cross-sectional study included 1321 patients, covering about 10% of diabetic population in this area. Among them, 4 (0.3%) lost plasma HbA1c data and 110 (8.3%) without information of diabetes history or treating histories were excluded from the analysis. Finally, 1207 (91.4%) T2DM individuals were included in this study.

The T2DM patients aged 65±9 years (30 to 90 years) and 420 were male (34.5%). The patients had T2DM disease duration of 8.1±1.0 years (min-max: 0.1-32.5 years) and HbA1c (%) of 7.61±0.08. Comorbidities such as hypertension (77.1%, 930/1207) and hyperlipidemia (22.7%, 274/1207) prevailed widely in this population. Among these offered information about changing life style and control diet before registration, 75% (520/692) followed the doctor's advice to control diet and improve lifestyle. Furthermore, 39 patients reported T2DM related diseases such as diabetes retinopathy (30 cases), diabetes peripheral neuropathy (3 cases), nephropathy or proteinuria (4 cases) and diabetes foot (2 cases).

Glucose lowering treatments patterns

According to self-reported information, 25 cases (2.1%, 25/1207) reported without glucose lowering treatments, 418 patients with only one antidiabetic regent. More than 60% (764/1207) patients managed with combination therapies and two-thirds (571/764) were two-drug combinations (Fig.1).

Among glucose lowering regents in this rural-urban fringe zone, SU, MET and AGI were the most frequently used OADs, especially for SU and MET, which accounted for 65% (785/1207) and 62% (749/1207) of the patients respectively. Also, 12% (150/1207) patients used short-term insulin (STI) as GLRs (Tab.1). For SU and STI, approximately one-third of them were single used for T2DM management, obvious higher than most of the regents except long-term insulin (LTI) (the most near percentage between SU and MET with $\chi 2=26.850$, $P<0.001$). AGI, TZD and DPP-4i were more used as combination therapies.

	Usage frequency	Monotherapy (%)*	Combination therapy			
			2	3	4	5
Oral antidiabetic drugs(OADs)						
SU	785	210(26.8)	449	114	11	1
MET	749	119(15.9)	459	154	16	1
AGI	194	11(5.7)	82	93	7	1
TZD	70	3(4.3)	25	36	6	0
Non-SU	68	10(14.7)	39	14	5	0
DPP-4i	51	2(3.9)	15	26	8	0
GLP-1RA	1	0(0.0)	0	0	1	0
Others	30	3(10.0)	3	17	7	0
Insulins						
STI	151	46(30.5)	54	42	8	1
LTI	62	14(22.6)	16	20	11	1

*:Percentage in monotherapy means single usage of this regent accounted for all of its usage.
T2MD, type 2 diabetes mellitus; SU, sulfonylurea; MET, metformin; AGI, α-glucosidase inhibitor; TZD, thiazolidinedione; Non-SU, None sulfonylurea; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; STI, short-term insulin; LTI, long-term insulin; Others including SGLT2i, sodium–glucose linked transporter 2 inhibitor and unspecific medicine in the investigation

Table 1: Treatment regimens for T2DM management in a rural-urban fringe zone in Suzhou city, Jiangsu Province, China.

T2DM, type 2 diabetes mellitus

*:Percentage in monotherapy means single usage of this regent accounted for all of its usage.

SU, sulfonylurea; AGI, alpha glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; Non-SU, None sulfonylurea; GLP-1RA ,Glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; STI, short-term insulin; LTI, long-term insulin; MET, metformin

SU and MET were the most commonly observed in combination usage for glucose lowering which accounted for 41%(489/1207) of patients under management (Tab.2). Among this combination, three quarters (371/489) were two-drug combination (Tab.3). SU combined with AGI was observed as the second with proportion of 11% (127/1207); however, more than a half (67/127) of this combination was in triple-drug combinations. And the AGI+MET combination accounted for more percentage (83%, 82/99) in the triple-drug combinations.

	SU	MET	AGI	TZD	Non-SU	DPP-4i	GLP-1RA	Others	STI	LTI
SU		489	127	40	4	21	1	9	13	10
MET	489		99	38	45	33	1	20	63	31
AGI	127	99		3	10	5	0	5	35	9
TZD	40	38	3		10	4	0	3	12	5
Non-SU	4	45	10	10		4	0	2	6	1
DPP-4i	21	33	5	4	4		1	7	8	8
GLP-1RA	1	1	0	0	0	1		0	0	0
Others	9	20	5	3	2	7	0		6	6
STI	13	63	35	12	6	8	0	6		23
LTI	10	31	9	5	1	8	0	6	23	

GLRs, glucose lowering regents; T2MD, type 2 diabetes mellitus; SU, sulfonylurea; MET, metformin; AGI, α-glucosidase inhibitor; TZD, thiazolidinedione; Non-SU, None sulfonylurea; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA ,glucagon-like peptide-1 receptor agonist; STI, short-term insulin; LTI, long-term insulin; Others including SGLT2i, sodium–glucose linked transporter 2 inhibitor and unspecific medicine in the investigation

Table 2: Combination matrix of GLRs for T2MD management in a rural-urban fringe zone in Suzhou city, Jiangsu Province, China.

GLRs, glucose lowering regents;T2DM, type 2 diabetes mellitus

SU, sulfonylurea; AGI, alpha glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor;Non-SU, None sulfonylurea; GLP-1RA ,Glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; STI, short-term insulin; LTI, long-term insulin; MET,metformin,

	2	3	4	5	Total
SU+ MET	371	108	9	1	489
SU+AGI	56	67	3	1	127
AGI+ MET	13	82	3	1	99
STI+ MET	29	29	4	1	63
NonSU+ MET	29	12	4		45
SU+TZD	13	23	4		40
TZD+ MET	2	30	6		38
STI+AGI	11	17	6	1	35
DPP-4i +MET	6	20	7		33
LTI+ MET	9	13	8	1	31
STI+LTI	3	12	7	1	23
SU+DPP-4i	3	13	5		21
Met+others	0	14	6		20
STI+SU	2	7	3	1	13
STI+TZD		4	8		12
LTI+SU	1	3	5	1	10
LTI+AGI		3	5	1	9

SU+others	2	5	2	9
STI+ DPP-4i	2	5	1	8
LTI+ DPP-4i	1	5	2	8
Others+ DPP-4i	1	4	2	7
STI+NonSU	3	2	1	6
LTI+others		4	2	6
STI+others		2	4	6

GLRs, glucose lowering regents; T2MD, type 2 diabetes mellitus; SU, sulfonylurea; MET,metformin; AGI, α-glucosidase inhibitor; STI, short-term insulin; Non-SU, None sulfonylurea; TZD, thiazolidinedione; DPP-4i, dipeptidyl peptidase-4 inhibitor; LTI, long-term insulin;
Others including GLP-1RA ,Glucagon-like peptide-1 receptor agonist and SGLT2i, sodium–glucose linked transporter 2 inhibitor

Table 3*:* Combination usages of GLRs for T2MD management in a rural-urban fringe zone in Suzhou city, Jiangsu Province, China

GLRs, glucose lowering regents;T2DM, type 2 diabetes mellitus

SU, sulfonylurea; AGI, alpha glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; Non-SU, None sulfonylurea; GLP-1RA ,Glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; STI, short-term insulin; LTI, long-term insulin; MET, metformin

Glucose lowering treatments and HbA1c control

Using HbA1c<7.0% as the T2DM control standard, the results showed that the control rate was 37.4% (451/1207, 95% CI 34.5% - 40.0%). Considering the therapy pattern of monotherapy or combination of regent numbers, it could be observed more regent numbers with less control rates for T2DM management. Single regent had control rate (95% CI) of 47.6% (199/418, 42.7%-52.5%), two-drug combination of 34.3%(196/571, 30.4%-38.4%), three-drug combination of 21.5%(37/172, 15.6%-28.4%) and four-drug combination of 15.0%(5/20,3.2%-37.9%). Specified for drug, for example, monotherapy of SU with control rate(95% CI) of 51.4% (108/210, 95% CI 44.5%-58.4%), nearly twenty percentage higher than that of combination therapy (32.9%,189/386, 95% CI 29.0%-36.9%)($\chi 2$=22.526, P<0.001). This was also true for treatments with MET and STI (Tab. 4).

	Monotherapy			Combination therapy			χ^2	*P*
	HbAc<7.0	HbAc≥7.0	Control rate(95% CI)	HbAc<7.0	HbAc≥7.0	Control rate(95% CI)		
SU	108	102	51.4(44.5-58.4)	189	386	32.9(29.0-36.9)	22.526	<0.001
MET	58	61	48.7(39.5-58.1)	196	434	31.1(27.5-34.9)	13.878	<0.001
STI	18	28	39.1(25.1-54.6)	24	81	22.9(15.2-32.1)	4.218	0.040
LTI	1	13	7.1(0.2-33.9)	9	39	18.8(8.9-32.6)	0.391*	0.531
Non-SU	4	6	40.0(12.2-73.8)	15	43	25.9(15.3-39.0)	0.290*	0.590
AGI	6	5	54.5(23.4-83.3)	56	127	30.6(24.0-37.8)	1.745*	0.186
TZD	2	1	66.7(9.4-99.2)	15	52	22.4(13.1-34.2)	Fisher**	0.144
DPP-4i	0	2	0.0(0.0-84.2)	8	41	16.3(7.3-29.7)	Fisher**	1.000

* Yates corrected chi square; **:Fisher exact

SU, sulfonylurea; MET, metformin; STI, short-term insulin; LTI, long-term insulin; Non-SU, None sulfonylurea; AGI, α-glucosidase inhibitor; TZD, thiazolidinedione;DPP-4i, dipeptidyl peptidase-4 inhibitor;

Table 4: Comparisons between monotherapy and combination therapy of the GLRs for T2DM management in a rural-urban fringe zone in Suzhou City, Jiangsu Province, China.

* Yates corrected chi square; **:Fisher exact

GLRs, glucose lowering regents;T2DM, type 2 diabetes mellitus

SU, sulfonylurea; AGI, alpha glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; Non-SU, None sulfonylurea; GLP-1RA ,Glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; STI, short-term insulin; LTI, long-term insulin; MET, metformin,

Among the most frequently combined used in combination therapies in T2DM management, two combinations of SU+MET and SU+AGI were with HbAc control rates of 33%(95%CI 29%-37%) and 35% (95%CI 26%-44%). Two combinations of AGI+ MET and STI+ MET were lower control rates of 28% (95%CI 19%-38%) and 21%(95%CI 11%-33%) (Fig.2 & 3).

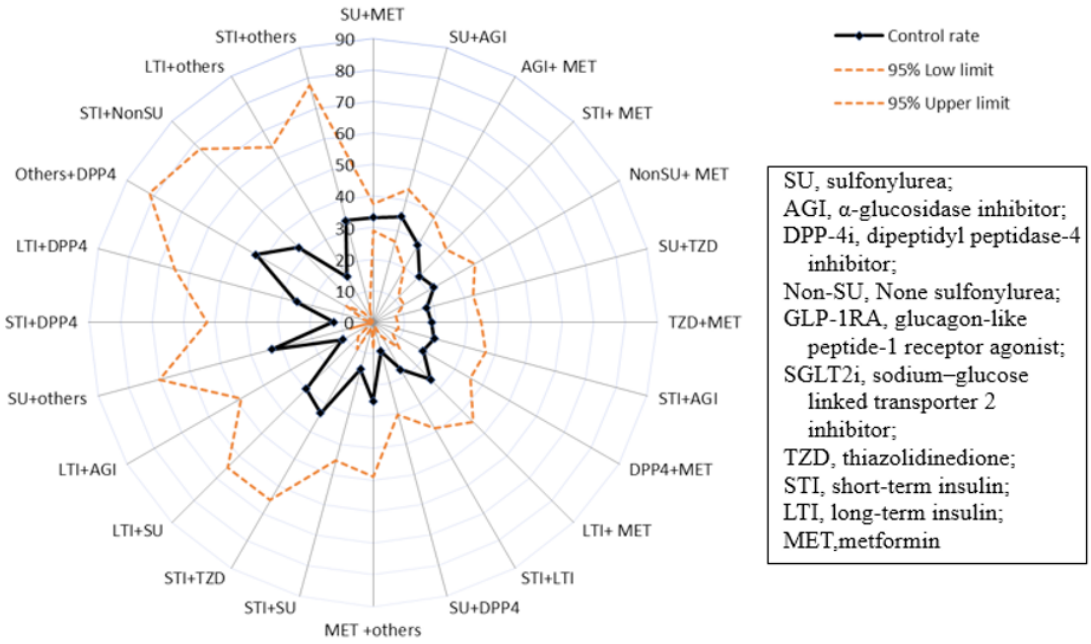

Figure 2: T2DM control rates for two-drug combinations in a rural-urban fringe zone in Suzhou City, Jiangsu Province, China.

SU, sulfonylurea; AGI, alpha glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; Non-SU, None sulfonylurea; GLP-1RA ,Glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; STI, short-term insulin; LTI, long-term insulin; MET, metformin,

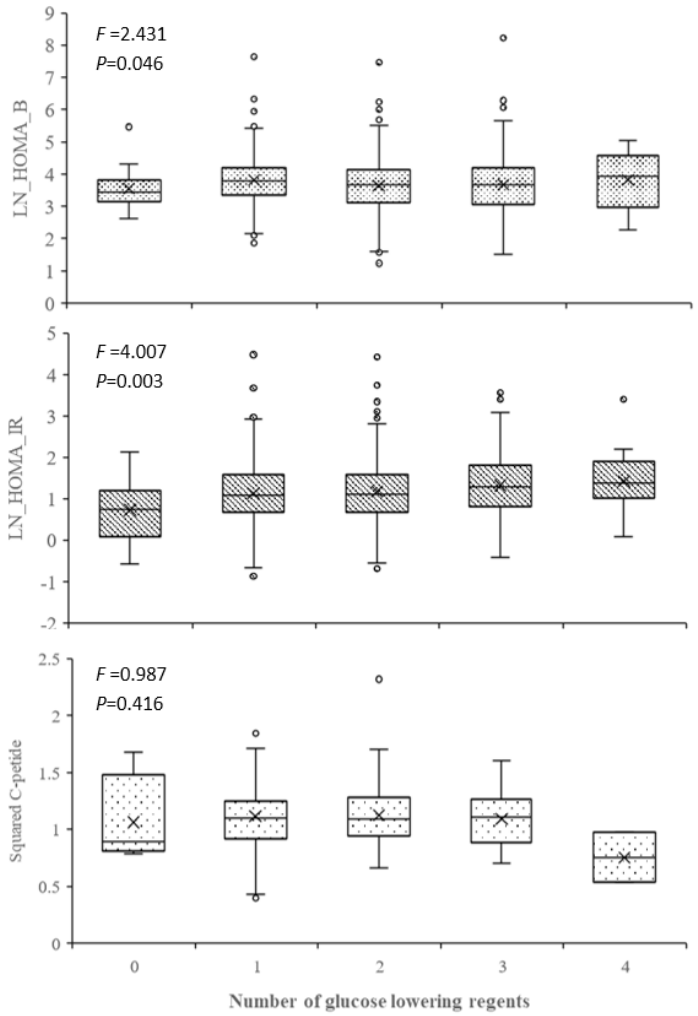

Figure 3: HOMA-β scores, HOMA-IR scores and C-peptide levels in T2DM patients treated with glucose lowering regents in a rural-urban fringe zone in Suzhou city, Jiangsu Province, China

HOMA-β means homeostasis model assessment of beta-cell function, HOMA-IR means homeostasis model assessment of insulin resistance

Glucose lowering treatments and islet function

HOMA-β scores, HOMA-IR scores and C-peptide levels were used to evaluate the function of islet in T2DM patients. The results showed that higher levels of HOMA-β and C-peptide in monotherapy of glucose lowering regents than the combinations, and HOMA-IR increased with number of combination regents. HOMA-β scores was in the levels 40.9±2.3(range: 3.4-3749.4), HOMA-IR was 3.2± 2.1(range: 0.4-88.2) and C-peptide 1.24 ± 0.08(range: 0.2-5.4) (Fig. 4).

SU as one insulin secretion promote regents, could increase 20% more HOMA-β levels when monotherapy used (untreated patients with HOMA-β: 35.0±1.9), however, almost no increase of this score when compared with combination (Tab. 5)

	Original Mean±SE				*Least-squares* Mean±SE*			
	Monotherapy	Combine therapy	*F*	*P*	Monotherapy	Combine therapy	*F*	*P*
HOMA-β	41.6±1.1	35.0±1.0	3.387	0.034	39.4±1.1	35.6±1.0	2.374	0.124
HOMA-IR	2.8±1.0	2.9±1.0	2.508	0.082	2.8±1.1	2.9±1.0	0.283	0.595
C-peptide	3.3±1.0	3.2±1.0	0.789	0.456	1.4±0.0	1.3±0.0	0.304	0.582

*Least-squares mean are means for groups that are adjusted for means of other factors in the model. In this paper, duration of T2DM was considered, and the process in SPSS as following (HOMA-β as example):

UNIANOVA LN_ HOMA-β BY monornotSU WITH SQDurationT2DM

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/INTERCEPT=INCLUDE

/EMMEANS=TABLES(monornotSU) WITH(SQDurationT2DM=MEAN) COMPARE ADJ(SIDAK)

/CRITERIA=ALPHA(0.05)

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Table 5: SU treatment and islet function evaluation in T2DM patients in a rural-urban fringe zone in Suzhou City, Jiangsu Province, China

Discussion

As an effective way to control blood glucose in patients with T2DM, antidiabetic regents play important roles in management. Studies show that strict control of blood glucose from the early stage can significantly reduce the risk of diabetic microangiopathy, which were confirmed by follow-up results with lower myocardial infarctions and deaths [1]. The Chinese guideline for the prevention and treatment of T2DM recommended metformin and life style intervention as the first-line measures [1]. However, in the rural-urban fringe zone in Suzhou city, about 62% (749/1207) of the patients followed the recommendation using metformin and the most frequently used antidiabetic regent was sulfonylurea with usage rate 65% (785/1207), which is near to neighbor Shanghai with a usage rate of 62.4%, far higher than the levels in other cities (40-50%) [3]. Also, the Chinese guideline suggested more GLRs combinations in T2DM managements for these with unsatisfactory control results, and results in this paper showed 64% (770/1207) of the patients used combinations, two-regent combination was 47% (571/1207) similar to that of its neighbor city Shanghai [3]. Thus, to implement better T2DM managements in this area, metformin and combination should be improved.

According to mechanisms, OADs are divided into drugs that mainly promote insulin secretion and drugs that lower blood sugar through other mechanisms. The former mainly includes SU, glinides, and DPP-4i, while drugs that lower blood sugar through other mechanisms mainly include MET, TZD, AGI and SGLT2i. The last decade experienced a surge in the number of GLRs that can be used to treat patients with T2DM. Accordingly, various medical associations have updated their guidelines for the treatment of diabetes in this new era. The most effective way to manage diabetes is to treat it with a combination therapy from the time of initial diagnosis and early combination therapy with diabetes/disease modifying drugs may improve the multiple pathophysiological abnormalities responsible for T2DM and its complications, thus resulting in the greatest long term benefits [6,9]. And the definition of diabetes/disease modifying drugs was proposed what makes T2DM treatment approaches simpler and therefore more useful in the primary care setting. Among DMDs, SGLT2i worked through their function in the kidney and GLP-1RAs probably through reduction in body weight. Yet, the diabetes/disease modifying drugs were seldom used in rural-urban fringe zone in Suzhou City, one case of GLP-1RA and none of SGLT2i. According to SIMPLE approach, for patient with T2DM not controlled on OADs, most patients should initiate SGLT2i and/or GLP-1RA [9]. Unique pattern that DPP-4i rather than metformin is predominantly used as the first-line treatment and SGLT2i use has increased consistently since their market entry, but remains low [4,5]. So, future management of T2DM in this area should increase the usage of novel regents issued recently, such as diabetes/disease modifying drugs including SGLT2i and/or GLP-1RA.

In this region, 37.4% (451/1207, 95% CI 34.5% - 40.0%) T2DM patients were with satisfactory control results (HbA1c<7.0%), far lower than the goal of management (55%). Usually, it is

considered that combinations of antidiabetic regents would works more effectively, however, according to this study, single regent had higher control rate, than two-drug combination or triple- or tetrad- drug combinations. This phenomenon was also observed in a combination of insulin and antidiabetic drugs [10]. This can be explained in two ways: first, before 2018, a sequential therapy strategy was carried out for T2DM management and the influence would still play a role in some places, especially in rural-urban fringe zone. In this condition, if T2DM uncontrolled with more drugs would be added instead of the effect and mechanism. The failure of single target approaches is the major challenge faced in T2DM treatment. Multitargeting is a promising approach for the treatment of T2DM as it includes multiple pathways [11]. Second, the combination had less effect and almost no new drugs were introduced in the patients of this area.

Different combinations may be caused by different patterns and habits. For example, in Italy, general practitioners, who play a major role in T2DM management, can only prescribe first-generation antidiabetic drugs, such as MET, SU, Non-SU, AGI, while the prescription of more recently marketed antidiabetic drugs, such as GLP-1RA, DPP-4i and SGLT2i, is restricted to diabetologist only [7]. SU and MET combination is 30% in Italy and decrease slightly from 2011 to 2017 [3], and this combination was the most commonly observed for glucose lowering which accounted for 41%(489/1207) of patients under management in this area. Among the most frequently combined used in combination therapies in T2DM management, two-drug combinations of SU+MET and SU+AGI were with HbAc control rates of 33% and 35%, higher than such combinations of AGI+MET (28%) and STI+MET(21%). With the number of drugs and classes of GLAs increasing rapidly, multiple combinations of therapies are available. The level of evidence required today for the introduction of new GLAs differs from what was required in the past, and no such information will be available for some of the older drug groups. And the experience of health care providers as well as patient experience with the older GLAs should not be dismissed [12]. It is suggested that the patient's pancreatic function should be evaluated before managements and the management plan should be formulated based on the HbA1c. [8] In this paper, though GLAs was used as monotherapy or combination, yet their effect should be considered carefully. For example, SU as one insulin secretion promote regents, could increase 20% more HOMA-β levels when monotherapy used (untreated patients with HOMA-β:35.0±1.9). So, in future management of T2DM, more suitable combinations should be developed depending on islet function evaluation.

In traditional Chinese medicine, T2DM is recognized as "marasmus and thirsty (in Chinses XiaoKe)" in traditional Chinese medical theory and the Chinese patent drugs (in Chinese ZhongCheng Yao) are widely used for preventing and treating according to the traditional Chinese medical theories such as "elimination thirsty, anti-weight loss and improve diuresis (SanXiao theory) ", "discrimination of yin deficiency type, yang deficiency type, and yin and yang dual-deficiency type (SanXing discrimination) " and "phased differentiation". The Guideline for the prevention and treatment of T2DM in China (2020 edition) issued in 2021 suggested that the Chinese patent drugs should play important roles in reducing blood glucose, improving symptoms and signs, and preventing complications [1]. Phytoconstituents are promising as they interact with multiple pathways simultaneously [11]. However, the reluctance to rely on phytoconstituents as the main therapy still remains as a limiting factor for such drugs to serve as mainstream interventions.

A few limitations of this study should be noted when interpreting its results. The study was based on data from registration claims, with limited information on the patients' clinical status. Furthermore, the reasons for combination therapies or adding other regents were not available. Although claims data provide accurate information on medication dispensation, the lack of these factors may have biased our assessment for the reasons. The paper based on prescription/dispensation data submitted by healthcare providers, so the patients' actual administration behaviors were unknown. Also, the dosage of the regents were not included in the paper because of there may be mistakes reported by patients themselves.

In conclusion, the glucose lowering treatment for T2DM management in the rural-urban fringe zone was a pattern almost following the recommendation by the authority, however, the effect of them was not as expected, and more glucose lowering regents would not raise the controlled rate. Thus, attentions should be paid to factors other than only drugs, including improving the education of diabetic patients, strengthening lifestyle intervention and blood glucose monitoring, improving the compliance, increasing the level of T2DM management ability and reducing the drug adjustment inertia of community doctors. Also, recently discovered regents should be included in the future managements.

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Conflict of interest: *No.*

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Approval of the research protocol*: Yes*

Informed Consent*:* Informed consent was obtained from all subjects and/or their legal guardians.

Approval date of Registry and the Registratio*n*

No. of the study/trial*:* Animal Studies: N/A

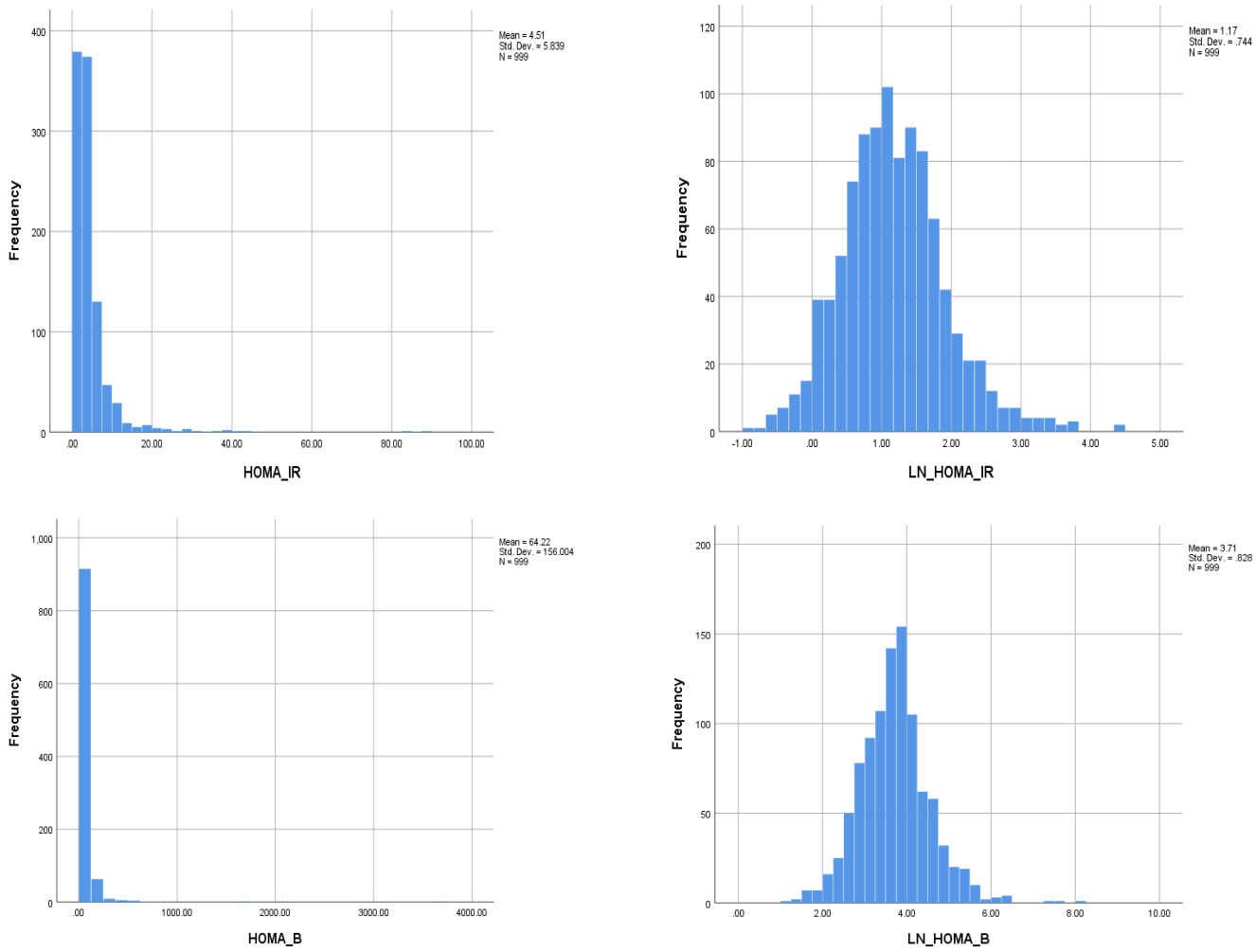
Data availability: The raw data has been uploaded. All data generated or analysed during this study are included in this published article [and its supplementary information files].

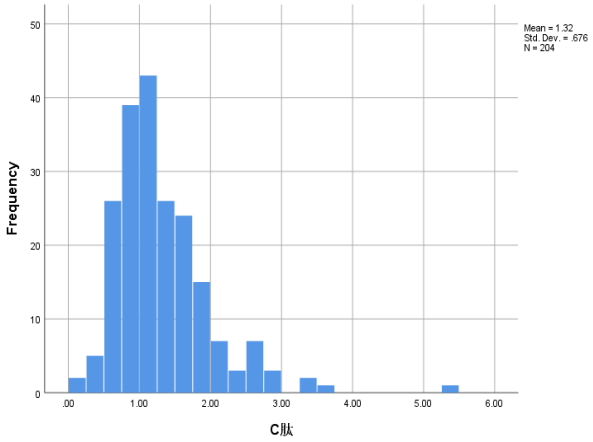
References

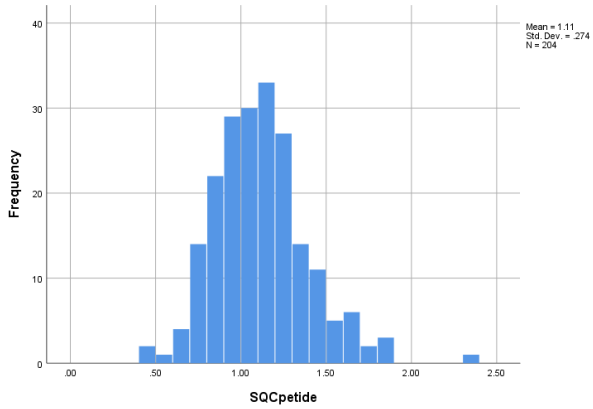
1. Chinese Diabetes Society. Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020edition). Chin J Diabetes Mellitus, 2021, 13(4):315-409.
2. Wang YZ,Chen XY, Xiao Q,et al. A survey on the treatment patterns of patients with type 2 diabetes mellitus in urban China. Chin J Dis Control Prev2018,22(3):222-225.
3. Ingrasciotta Y, Bertuccio MP, Crisafulli S, Ientile V, Muscianisi M, L'Abbate L, Pastorello M, Provenzano V, Scorsone A, Scondotto S, Trifirò G. Real World Use of Antidiabetic Drugs in the Years 2011-2017: A Population-Based Study from Southern Italy. Int J Environ Res Public Health. 2020 Dec 18;17(24):9514.
4. Tajima A, Tobe K, Eiki JI, et al. Treatment patterns and satisfaction in patients with type 2 diabetes newly initiating oral monotherapy with antidiabetic drugs in Japan: results from the prospective Real-world Observational Study on Patient Outcomes in Diabetes (RESPOND). BMJ Open Diabetes Res Care. 2022 Dec;10(6):e003032.
5. Kameda T, Kumamaru H, Nishimura S, Kohsaka S, Miyata H. Use of oral antidiabetic drugs in Japanese working-age patients with type 2 diabetes mellitus: dosing pattern for metformin initiators. Curr Med Res Opin. 2020 May;36(5):749-756.
6. Weinberg Sibony R, Segev O, Dor S, Raz I. Drug Therapies for Diabetes. Int J Mol Sci. 2023 Dec 5;24(24):17147.
7. Giorda CB, Manicardi V, Diago Cabezudo J. The impact of diabetes mellitus on healthcare costs in Italy. Expert Rev Pharmacoecon Outcomes Res. 2011 Dec;11(6):709-19.
8. Liu J,Zhu DL, Primary diabetes Prevention and Treatment Group, diabetes Branch, Chinese Medical Association. Chinese experts' consensus on the treatment of type 2 diabetes with oral hypoglycemic drugs and starting insulin at the grass-roots level. Chin J Diabetes May 2022,Vol. 30(5):321-330
9. Mosenzon O, Del Prato S, Schechter M, Leiter LA, Ceriello A, DeFronzo RA, Raz I. From glucose lowering agents to disease/diabetes modifying drugs: a "SIMPLE" approach for the treatment of type 2 diabetes. Cardiovasc Diabetol. 2021 Apr 28;20(1):92.
10. Dong Q, Huang J, Liu S, Yang L, Li J, Li B, Zhao X, Li Z, Wu L. A survey on glycemic control rate of type 2 diabetes mellitus with different therapies and patients' satisfaction in China. Patient Prefer Adherence. 2019 Jul 31;13:1303-1310.
11. Borse SP, Chhipa AS, Sharma V, Singh DP, Nivsarkar M. Management of Type 2 Diabetes: Current Strategies, Unfocussed Aspects, Challenges, and Alternatives. Med Princ Pract. 2021;30(2):109-121.
12. Mosenzon O, Pollack R, Raz I. Treatment of Type 2 Diabetes: From "Guidelines" to "Position Statements" and Back: Recommendations of the Israel National Diabetes Council. Diabetes Care. 2016 Aug;39 Suppl 2:S146-53.

Supplement Figure 1 Data distribution for original data and transformed data

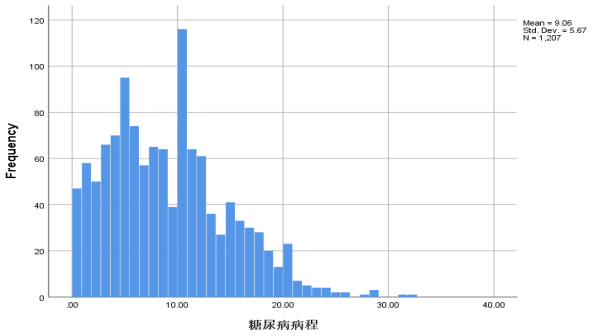
Original distribution **Transformed distribution**

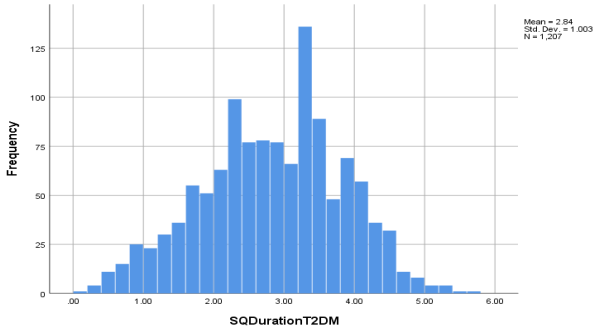






C peptide(μU/mL) *SQRT(C peptide)*





Disease duration(Years) *SQRT(Disease duration)*