

Comparative Association of Basal and Basal-Prandial Insulin Regimens on Remnant Cholesterol and Lipid Profiles in Patients with Type 2 Diabetes Mellitus

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Background: The relationship between remnant cholesterol (RC) and insulin therapy is a critical issue in public health. Each insulin regimen used in T2DM patients can have different effects on lipid metabolism. However, clinical evidence comparing the effects of basal insulin and combined basal-prandial insulin on RC levels is limited.

Purpose: To investigate and compare the association between basal and basal-prandial insulin regimens on RC and lipid profiles of patients with T2DM using a cross-sectional measurement.

Methods: The study involved 118 eligible T2DM patients receiving either basal or combined basal-prandial insulin at Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia. Bivariate analysis was performed using the Chi-square test. Multiple logistic regression was used to identify independent factors associated with RC levels.

Results: The study reveals that the proportion of patients with normal RC level was significantly greater in the basal-prandial group than in the basal insulin group (49.2% and 30.5%, respectively, $p = 0.039$). Bivariate analysis showed that the type of insulin regimens was significantly associated with RC (OR 0.454; 95% CI 0.214–0.965). In multivariate analysis, the association was no longer significant ($p = 0.375$), indicating that other factors, such as duration of DM and BMI, contributed to the change in the strength of the association. On the other hand, normal high-density lipoprotein cholesterol (HDL-C) remained an independent protective factor against normal RC (OR, 4.898; 95% CI, 1.484–16.159; $p = 0.009$).

Conclusion: Compared to basal insulin therapy alone, the combination of basal-prandial insulin regimen was more beneficial in maintaining normal RC levels, although its effects were partially mediated by HDL-C, DM duration, and BMI. Therefore, clinical decisions aimed at improving RC levels in T2DM should consider overall metabolic factors, including HDL-C status, DM duration, and adiposity, rather than on insulin regimen type alone.

Keywords: cholesterol, glycosylated hemoglobin, hyperglycemia, insulin regimen, metabolic disorders, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is now a growing global health challenge, as the number of affected people is projected to grow continually from 588.7 million people in 2024 to 852.5 million in the coming two decades.¹ Oral anti-hyperglycemic drugs (OADs) are typically the first-line approach in T2DM. However, studies have reported that oral agents cannot fully counter rising insulin resistance or the progressive loss of β -cell function. As a result, many patients eventually fail to sustain glycemic control.² When oral medication is no longer adequate, insulin therapy becomes one of

the potential approaches. Although newer agents such as GLP-1 receptor agonists and SGLT2 inhibitors provide additional cardiometabolic benefits, insulin remains essential in many patients with type 2 diabetes.^{3,4}

The primary goal of insulin therapy is to regulate blood glucose levels and minimize the risk of long-term complications. Numerous studies have demonstrated that insulin therapy effectively reduced hemoglobin A1c (HbA1c), fasting glucose, and postprandial glucose.^{3,5} However, its impact on lipid metabolism remains a topic of debate. Pathophysiologically, insulin plays a crucial role in lipid metabolism by stimulating lipogenesis and regulating fat storage through the modulation of enzymes and lipoproteins involved in these processes.⁶ Nonetheless, insulin therapy can be metabolically ineffective in a subset with poorly controlled T2DM when adequate glycemic targets are not achieved. Kartz et al⁷ showed that although insulin modestly attenuated increases in low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), and non-esterified fatty acids, these benefits were largely HbA1c-dependent and insufficient to halt the progression of atherogenic dyslipidemia. Moreover, systemic inflammation, particularly high-sensitivity C-reactive protein (hs-CRP), continued to rise after insulin initiation, indicating persistent cardiovascular risk despite treatment. Other studies support that lipid response to insulin therapy is strongly influenced by the degree of underlying insulin resistance. In individuals with marked insulin resistance, insulin may not fully normalize lipid metabolism, leading to elevated triglyceride (TG) levels, hepatic fat accumulation, and alterations in lipoprotein metabolism.⁷⁻⁹ As a result, conventional lipid parameters may not fully capture the residual atherogenic risk that remains despite glucose improvement.

Remnant cholesterol (RC) is the cholesterol content within lipoprotein remnants after TG is catabolized by lipoprotein lipase (LPL). In clinical and epidemiological studies, RC is commonly calculated from the standard lipid profile using the formula $RC = TC - HDL-C - LDL-C$. Unlike total cholesterol (TC) or LDL-C, these remnant particles are cholesterol-rich, can penetrate the intima of blood vessels, trigger inflammation, and play a key role in the formation of atherosclerotic plaques.¹⁰ Several studies have shown that high RC levels are strongly associated with an increased risk of cardiovascular disease in patients with T2DM.^{11,12} Cohort data show that RC provides superior discriminatory power for cardiovascular risk because it reflects the residual atherogenic load that persists despite normal or controlled LDL-C levels.¹³ In these analyses, RC showed a stronger and more consistent association with incident cardiovascular events than traditional lipid parameters, underscoring that triglyceride-rich remnant particles contribute to plaque formation through pathways that are not captured by standard cholesterol measurements. Recent studies suggest that RC reflects residual atherogenic risk and broader cardiometabolic dysfunction even when LDL-C is controlled.¹⁴ Therefore, RC has emerged as a more specific, non-conventional lipid marker in assessing the risk of atherosclerosis in patients with T2DM.

Different types of insulin regimens exert varying effects on lipid metabolism, including RC levels. Basal (long-acting) insulin acts by continuously suppressing hepatic glucose production, thereby stabilizing fasting plasma glucose levels and reducing the metabolic strain imposed by chronic hyperglycemia. This steady background insulin level also inhibits lipolysis, reducing excess free fatty acid flux to the liver and supporting improvements in both glucose and lipid homeostasis. Through this sustained 24-hour mechanism, basal insulin provides a metabolic foundation that facilitates more reliable overall glycemic control.¹⁵ Basal insulin primarily targets fasting glycemia, whereas prandial insulin controls postprandial glucose excursions. Their combination more closely mimics physiological insulin secretion.¹⁶ The combined basal-prandial insulin integrates these complementary actions, enabling simultaneous regulation of both fasting and postprandial glucose fluxes and most closely replicating the biphasic pattern of endogenous insulin secretion, thereby achieving superior physiological glycemic coverage across the diurnal cycle.^{17,18}

Most studies have focused on how insulin affects blood glucose or conventional lipid profiles, such as TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), and TG.^{19,20} Cindro et al²¹ reported that basal insulin therapy significantly reduces glycemic variability, which is closely associated with improvements in vascular function, as reflected by decreased arterial stiffness. Importantly, this stabilization of glucose fluctuations was accompanied by favorable alterations in lipid profiles, including significant reductions in TC, LDL-C, and TG. Yamada et al²² demonstrated that insulin lispro, a prandial insulin analogue, significantly lowers 1–2 hour postprandial glucose increments and slightly rises both LDL-C and HDL-C, suggesting that prandial insulin timing influences not only glycemic excursions but also acute lipoprotein dynamics after meal intake. Yamaguchi et al²³ reported that two weeks of basal-prandial insulin therapy reduces both cholesterol synthesis

(lathosterol) and absorption (campesterol, sitosterol) in patients with T2DM, through the suppressed activation of sterol regulatory element-binding protein (SREBP) and upregulated LXR-ABCG5/8 cholesterol-efflux pathway.

In contrast to the classical lipid parameters, RC rarely receives attention, though its role in atherosclerosis may be more prominent.²⁴ Increased postprandial glucose itself has been associated with elevated postprandial lipemia. Postprandial hyperglycemia promotes postprandial lipemia by suppressing insulin-mediated activation of LPL, thereby slowing the hydrolysis and clearance of chylomicron and VLDL remnants. Simultaneously, elevated glucose increases hepatic VLDL production through enhanced free fatty acid (FFA) influx and de novo lipogenesis, expanding the pool of triglyceride-rich lipoproteins (TRLs). Hyperglycemia-induced oxidative stress and endothelial dysfunction further reduce endothelial LPL activity and impair hepatic remnant uptake. Together, these disturbances accelerate the accumulation of cholesterol-rich remnant particles and drive elevations in RC.²⁵ However, data on the relationship between insulin regimen type and RC levels in T2DM patients remain limited, highlighting the urgency for further research. To the best of the authors' knowledge, clinical evidence specifically comparing the effects of basal insulin and combined basal-prandial insulin on RC levels in T2DM patients has not been reported yet.

Despite growing recognition of remnant cholesterol as an important marker of residual cardiovascular risk, most clinical studies have focused on conventional lipid parameters and the influence of different insulin regimens on remnant cholesterol levels remains poorly understood. To date, no clinical study has directly compared basal insulin and combined basal-prandial insulin regimens in relation to remnant cholesterol levels in patients with T2DM.

Therefore, this study was conducted to examine the association between basal and combined basal-prandial insulin regimens on RC levels in patients with T2DM and to identify factors influencing this relationship. The results are expected to contribute to the understanding of the mechanisms by which insulin regimens affect non-conventional lipid metabolism. Furthermore, it may also enrich clinical evidence for preventing cardiovascular complications in the diabetic population.

Methods

Study Participants

This multi-disciplinary cross-sectional study has been reviewed and approved by the Research Ethics Committee of Padjadjaran University with ethical approval document number 652/UN6.KEP/EC/2025 dated July 30, 2025, signed by Dr. med. Muhammad Hasan Bashari, dr., M.Kes., involving 118 patients with T2DM who visited the endocrine polyclinic of Dr. Wahidin Sudirohusodo General Hospital in Makassar, Indonesia, from August to November 2025. The inclusion criteria were as follows: (1) T2DM diagnosis based on the 1999 World Health Organization diagnostic criteria; (2) adults (30–59 years) and elderly (60–79 years) with T2DM who had HbA1c levels $\geq 6.5\%$; (3) currently receiving basal insulin regimens or a combination of basal-prandial insulin for at least 3 months, to ensure a relative metabolic steady state and minimize the influence of recent treatment adjustments on lipid parameters including remnant cholesterol; (4) having standard lipid profile laboratory data (TC, HDL-C, LDL-C) in the last 3 months; and (5) willing to participate in the study by signing an informed consent. The exclusion criteria were: (1) patients under treatment of other additional hypoglycemic drugs in the last 3 months, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, fibrates, or statins; (2) advanced kidney disease (eGFR < 30 mL/min/1.73 m² or undergoing dialysis); (3) severe liver dysfunction (ALT or AST > 5 times the normal limit); (4) patients using systemic corticosteroids in the last month; and (5) patients in pregnancy or lactating period. Information regarding recent insulin dose adjustments or acute intercurrent illnesses that may have transiently affected lipid levels was not systematically available from the medical records.

Medical Data and Biochemical Measurements

General participant data, such as age, gender, body mass index (BMI), DM duration, smoking history, and blood pressure, were collected from medical records. The type of insulin, basal or combined basal-prandial regimens, was also recorded. Laboratory tests included a lipid profile (TC, LDL-C, HDL-C) analyzed using the Cobas c 111 (Roche, Germany). RC levels were calculated from the lipid profile results based on the following equation:

$$RC(mg/dL) = TC(mg/dL) - HDL-C(mg/dL) - LDL-C(mg/dL)$$

Where:

RC is remnant cholesterol

TC is total cholesterol

HDL-C is high-density lipoprotein cholesterol

LDL-C is low-density lipoprotein cholesterol

Because remnant cholesterol is calculated from TC, HDL-C, and LDL-C, inclusion of these lipid components in multivariable regression models may introduce mathematical coupling and overadjustment; therefore, associations involving these variables were interpreted with caution.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 33.0 (IBM Corp., Armonk, NY, USA). Most variables in this study were analyzed as categorical and are presented as numbers (n) and percentages (%). Comparisons between the basal and combined basal–prandial insulin regimen groups were performed using the Chi-square test. The variables analyzed included patient characteristics (gender, age, BMI, duration of diabetes, smoking history, and blood pressure), lipid profiles (LDL-C, HDL-C, and RC), and insulin regimens (basal and combined basal–prandial). Because this was a cross-sectional study, all analyses were interpreted as associations rather than causal effects.

In bivariate analysis, variables with a *p*-value < 0.20 were entered into a binary logistic regression model. This cut-off was used to ensure potential factors were not missed. In multivariate analysis, only variables with a *p*-value < 0.05 were considered statistically significant. Logistic regression results are reported as odds ratios (OR) with 95% confidence intervals (CI). Given the sample size, the number of variables included in the multivariable model was carefully limited to reduce the risk of model overfitting. The modest sample size (*n* = 118) may have limited the events-per-variable ratio in multivariable models. Therefore, regression results should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

Results

Clinical Characteristics of the Study Subjects

Table 1 presents the clinical characteristics of T2DM patients according to the type of insulin regimens. Compared with the basal insulin therapy group (*n* = 59), the combined basal–prandial insulin therapy group (*n* = 59) showed a significantly higher proportion of patients with normal RC levels (49.2% vs 30.5%, *p* = 0.039). When analyzed as a continuous variable, median RC levels were 54 mg/dL in the basal group and 39 mg/dL in the basal–prandial group,

Table 1 Comparison of T2DM Patients' Characteristics in Both Insulin Regimen Groups

Variables	Category	Insulin Regimens				p-value
		Basal		Basal-Prandial Combination		
		N	%	n	%	
Gender	Male	31	52.5	34	57.6	0.579
	Female	28	47.5	25	42.4	
Age	Mature (30–59 years)	28	47.5	28	47.5	I
	Elderly (60–79 years)	31	52.5	31	52.5	
BMI	Non-Obesity (< 25 kg/m ²)	34	57.6	32	54.2	0.711
	Obesity (≥ 25 kg/m ²)	25	42.4	27	45.8	

(Continued)

Table 1 (Continued).

Variables	Category	Insulin Regimens				p-value
		Basal		Basal-Prandial Combination		
		N	%	n	%	
DM Time	<10 Years	38	64.4	31	52.5	0.191
	>10 Years	21	35.6	28	47.5	
Smoke	Yes	25	42.4	24	40.7	0.852
	No	34	57.6	35	59.3	
Blood pressure	Normal (< 120/80 mmHg)	15	25.4	19	32.2	0.416
	Abnormal (≥ 120/80 mmHg)	44	74.6	40	67.8	
TC	Normal (< 200 mg/dl)	25	42.4	32	54.2	0.197
	Abnormal (≥ 200 mg/dl)	34	57.6	27	45.8	
LDL-C	Normal (< 130 mg/dl)	40	67.8	37	62.7	0.562
	Abnormal (≥ 130 mg/dl)	19	32.2	22	37.3	
HDL-C	Normal Male (> 40 mg/dl) Female (> 50 mg/dl)	10	16.9	16	27.1	0.183
	Abnormal Male (≤ 40 mg/dl) Female (≤ 50 mg/dl)	49	83.1	43	72.9	
RC	Normal (< 30 mg/dl)	18	30.5	29	49.2	0.039*
	Abnormal (≥ 30 mg/dl)	41	69.5	30	50.8	

Notes: All study variables were categorical and shown as numbers (n) and percentages (%). Comparisons between the insulin regimen groups were made using the Chi-square test. Analyzed variables included patient characteristics (gender, age, BMI, diabetes duration, smoking history, blood pressure), lipid profiles (LDL-C, HDL-C, RC), and insulin regimens (basal, basal-prandial). *Indicates statistical significance at $p < 0.05$.

Abbreviations: BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RC, remnant cholesterol.

with a statistically significant difference between groups. Meanwhile, most other clinical variables, including gender, age, BMI, duration of DM, smoking history, blood pressure, and other lipid profiles (TC, LDL-C, and HDL-C), did not show significant differences between groups ($p > 0.05$).

Univariate Analysis

As shown in Table 1, the majority of patients in both groups were male, elderly (≥ 60 years), non-obese (≥ 25 kg/m²), had diabetes for <10 years, and had abnormal blood pressure ($\geq 120/80$ mmHg). The lipid profiles of the patients revealed that most had abnormal HDL-C levels (for males ≤ 40 mg/dL and for females ≤ 50 mg/dL) and abnormal RC levels (≥ 30 mg/dL). These findings indicate that lipid abnormalities are a common characteristic in T2DM patients receiving insulin regimens.

Bivariate Analysis

Table 2 shows the RC values and the significance of differences between T2DM patients based on the type of insulin regimens. Bivariate analysis showed a significant difference in the RC variable between the basal and combined basal-prandial groups ($p = 0.039$). Patients using basal-prandial therapy had a higher chance of maintaining normal RC levels compared to patients using basal insulin (OR 0.454; 95% CI 0.214–0.965). Other variables, including gender, age, BMI,

Table 2 RC Value and Significance of the Difference Between the Insulin Regimen Groups

Insulin Regimens	RC Value				p-value Chi-Square	OR	95% CI
	Normal		Abnormal				
	N	%	n	%			
Basal	18	30.5	41	69.5	0.039*	0.454	0.214–0.965
Basal-Prandial Combination	29	49.2	30	50.8			

Notes: All variables in this study were categorical and presented as numbers (n) and percentages (%). Comparisons between the basal and combined basal-prandial insulin regimen groups were performed using the Chi-square test. The variables analyzed included insulin regimens (basal and combined basal-prandial) and remnant cholesterol. *Indicates statistical significance at $p < 0.05$.

Abbreviations: RC, remnant cholesterol; OR, odds ratio; 95% CI, 95% confidence interval.

duration of DM, smoking status, blood pressure, TC, LDL-C, and HDL-C, did not show a significant association with the type of insulin regimens ($p > 0.05$). RC values are also presented as continuous variables in Table 1 to provide additional distributional information beyond the normal/abnormal category.

Multivariate Analysis

Table 3 shows the relationship between insulin regimens and RC levels after controlling for several variables. Multiple logistic regression analysis was performed with RC category (normal vs abnormal) as the dependent variable, while gender, age, BMI, duration of DM, smoking history, blood pressure, insulin regimen type, TC, LDL-C, and HDL-C were included as covariates. The results showed that most variables were not significantly associated with RC ($p > 0.05$). In contrast, HDL-C was statistically associated with RC ($p = 0.009$). Patients with normal HDL-C had a 4.9 times greater chance of maintaining normal RC (OR 4.898; 95% CI 1.484–16.159). However, this association should be interpreted cautiously as HDL-C is metabolically and mathematically related to RC, which may partly explain the strength of this relationship.

Table 4 summarizes the factors that strongly influence the association between insulin regimens and RC levels. The analysis reveals that although the type of insulin regimens was significant in the bivariate analysis, this significance was

Table 3 The Relationship Between Insulin Regimens and RC Levels After Controlling

Variables	B	SE	Wald	p-value	OR	95% CI
Gender	−0.392	0.687	0.326	0.568	0.676	(0.176–2.598)
Age	0.178	0.481	0.136	0.712	1.194	(0.465–3.065)
BMI	−0.216	0.471	0.211	0.646	0.806	(0.320–2.029)
DM Time	0.179	0.487	0.135	0.713	1.196	(0.451–3.103)
Smoke	0.019	0.677	0.001	0.978	1.019	(0.271–3.838)
Blood pressure	0.302	0.540	0.314	0.576	1.353	(0.470–3.895)
Insulin	−0.423	0.477	0.786	0.375	0.655	(0.257–1.668)
TC	20.996	7344.071	0.000	0.998	131982069	0.000
LDL-C	−21.502	7344.071	0.000	0.998	0.000	0.000
HDL-C	1.589	0.609	6804	0.009*	4.898	1.484–16.159

Notes: Multiple logistic regression analysis was performed with RC as the dependent variable and other variables as covariates. The variables analyzed included patient characteristics (gender, age, BMI, duration of diabetes, smoking history, and blood pressure), lipid profiles (LDL-C, HDL-C, and RC), and insulin regimens (basal and combined basal-prandial). TC and LDL-C showed extreme values due to multicollinearity and were excluded from the model interpretation. *Indicates statistical significance at $p < 0.05$.

Abbreviations: BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RC, remnant cholesterol.

Table 4 The Key Factors Affecting Insulin Regimens and RC Levels Association

Crude OR	p-value	OR	95% CI	OR Change
Insulin	0.040	0.454	(0.214–0.965)	
<i>Adjusted</i>				
(+) Gender	0.032	0.432	(0.201–0.929)	–4.8
(+) Age	0.040	0.453	(0.213–0.963)	0
(+) BMI	0.042	0.457	(0.215–0.973)	5.8*
(+) DM Time	0.041	0.453	(0.212–0.967)	8*
(+) Smoking	0.041	0.453	(0.212–0.967)	0.9
(+) Blood Pressure	0.041	0.455	(0.214–0.968)	0.4
(+) TC	0.053	0.473	(0.221–1.010)	4.4
(+) LDL-C	0.049	0.450	(0.203–0.995)	–10.1
(+) HDL-C	0.071	0.491	(0.227–1.062)	3.8

Notes: Multiple logistic regression analysis was performed with RC as the dependent variable and other variables as covariates. The crude OR value indicates the initial association between insulin regimens and RC levels before adjustment for covariate variables. After adjustment (adjusted model), the change in odds ratio (Δ OR) value was used to assess the influence of each covariate variable on the strength of the association between insulin regimens and RC levels. The variables analyzed included patient characteristics (gender, age, body mass index/BMI, duration of diabetes, smoking history, and blood pressure) and lipid profile (TC, LDL-C, and HDL-C). *Indicates statistical significance at $p < 0.05$.

Abbreviations: BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RC, remnant cholesterol.

lost after controlling for other variables ($p = 0.375$). In this table, the “change in OR” refers to the relative change in the odds ratio for the insulin regimen after the sequential inclusion of individual covariates into the model, and does not represent separate final regression models. Based on the analysis of changes in the odds ratio (OR), duration of diabetes (+8%) and BMI (+5.8%) were the two factors with the strongest influence on the association between the type of insulin regimen and RC levels. This suggests that overall metabolic burden plays a more prominent role in determining RC status than insulin regimen type alone.

Discussion

In this study, we investigated the association between two insulin regimens, basal insulin and combined basal-prandial insulin, on RC levels in patients with T2DM. Patients with T2DM using insulin therapy, whether basal or combination, share similar characteristics: older age, non-obese BMI, uncontrolled blood pressure, and low HDL-C levels. These features reflect underlying metabolic disturbances in advanced type 2 diabetes. Age contributes to impaired insulin receptor substrate-1 (IRS-1) signalling and reduced glucose transporter-4 (GLUT-4) translocation, alongside oxidative stress, glucotoxicity, and lipotoxicity that accelerate beta-cell dysfunction.^{26,27} Non-obese BMI, particularly common in Asian populations, often indicates excess visceral adiposity, which increases free fatty acid (FFA) release and activates protein kinase C (PKC), leading to chronic low-grade inflammation and greater insulin resistance.^{28–31} Uncontrolled blood pressure arises because insulin resistance promotes endothelial dysfunction and activates the renin–angiotensin system,³² consistent with findings that insulin-treated patients tend to be older and more hypertensive.³³ Low HDL-C reflects disrupted lipid metabolism characteristic of type 2 diabetes, including reduced reverse cholesterol transport and increased RC accumulation that amplifies vascular inflammation and atherogenesis.^{34,35} These interconnected mechanisms indicate that patients

requiring insulin are already in a more severe metabolic state, highlighting the need for comprehensive cardiometabolic management beyond glycemic control.

The results showed that patients using combined basal-prandial therapy had a higher proportion of normal RC levels than those using basal insulin alone. However, this association was not statistically significant after multivariable adjustment, indicating that the insulin regimen was not independently associated with RC. These findings are consistent with the hypothesis that postprandial glucose control, in addition to fasting glucose, is an important factor in reducing the accumulation of atherogenic remnant particles. In a methodologically different approach, intensive basal-prandial (detemir-aspart) insulin therapy results in a clear reduction in TG from 41.3 h mmol/L to 29.5 h mmol/L and directly measured remnant lipoprotein-cholesterol (RemL-C) from 210.7 h mmol/L to 127.1 h mmol/L, following short-term inpatient glycemic optimization.³⁶ In another study, a 14-day intensive combined insulin therapy of aspart before meals together with bedtime neutral protamine hagedorn (NPH) caused a substantial reduction in ApoB-48 from 6.1 to 4.6 µg/mL and a parallel decline in chylomicron-TG in patients with poorly controlled T2DM.³⁷ ApoB-48 is the structural hallmark of chylomicrons and their RC, therefore, this finding indicates that meal-coupled insulin action is highly effective in suppressing intestinal lipoprotein output and reducing remnant-related burden, even over a short duration. The observed decrease in ApoB-48 also correlated significantly with reductions in small dense LDL-C, underscoring the tight metabolic linkage between chylomicron-remnant handling and downstream atherogenic particle remodeling.³⁸ A similar aspart-NPH insulin regimen given over 12 weeks has been shown to improve LDL particle characteristics, shifting the profile toward larger, less atherogenic LDL particles after intensification.³⁹ This improvement occurred alongside enhanced LPL activity and reduced TG, key metabolic shifts that limit the formation of small dense LDL. Because small dense LDL is closely linked to elevated RC and impaired remnant clearance, these treatment-related changes suggest that optimized insulin therapy indirectly supports a more favorable remnant-related lipid pattern. These mechanistic findings provide biological plausibility, suggesting that insulin regimens incorporating prandial components could influence RC dynamics through postprandial metabolic pathways. However, in the present study, insulin regimen type was not independently associated with RC levels after multivariable adjustment, indicating that this potential effect may be overshadowed by other metabolic determinants. These mechanistic observations provide biological plausibility but do not demonstrate a causal effect of insulin regimen on RC in this cross-sectional study.

This study found that the most commonly used insulin in the basal insulin therapy group was insulin detemir (Levemir, 61%), while in the basal-prandial combination group, the majority of patients used insulin degludec/aspart (IDegAsp; Ryzodeg, 67.8%). Basal insulins such as detemir, glargine, and degludec function to suppress hepatic glucose production during the fasting period. However, the use of basal insulin alone is not optimal in controlling postprandial glucose.^{40,41} As a result, excess glucose substrate after meals increases hepatic lipogenesis and the synthesis of triglyceride-rich VLDL, which in turn causes an increase in RC levels and a decrease in HDL-C.¹⁵ An integrated analysis of six IMAGINE trials showed distinct lipid effects across basal insulin types. Standard basal insulins, glargine and NPH, produced stable or modestly improved TG and minimal changes in LDL-C or HDL-C. In contrast, the hepato-preferential basal insulin peglispro (BIL) demonstrated a unique metabolic pattern, with TG remaining stable in insulin-naïve patients but increasing by roughly 15–25% in those previously using insulin. This effect reversed upon cessation of BIL therapy.⁴² Another study also reported the superior effects of BIL compared to NPH and glargine insulin.⁴³ These divergent responses underscore that basal insulin formulations have distinct effects on TRLs, a pathway closely linked to the remnant-related lipid dynamics examined in this study. Sub-analysis of the Study of Once-Daily Levemir (SOLVE) programs' data showed that initiating once-daily insulin detemir in patients with T2DM produced meaningful improvements in glycemic control without compromising the routine lipid profile.⁴⁴ Over 24 weeks of real-world therapy, fasting glucose, HbA1c, and body weight improved, while TG, LDL-C, and HDL-C remained generally stable under standard clinical monitoring. This pattern supports the broader view that effective basal insulin replacement contributes to a more favorable lipid metabolic milieu. Although not directly reporting the RC value, the study by Bunck et al provided important insight into how basal insulin therapy influences remnant-related lipoprotein metabolism.⁴⁵ After 52 weeks of insulin glargine treatment, the postprandial ApoB-48 excursions showed minimal change from baseline (LS mean change: -4.3 µg·h/mL). This modest effect suggests that basal insulin alone has limited ability to suppress postprandial lipoprotein secretion or enhance remnant clearance. Pathophysiologically, this explains why the use of basal insulin alone

can reduce fasting glucose production but does not prevent the formation of atherogenic RC particles. It is important to recognize that the distribution of specific insulin formulations differed between groups. Detemir was predominant in the basal group and IDegAsp in the basal–prandial group. These pharmacologic differences may influence lipid metabolism independently of regimen structure and therefore could confound comparisons attributed solely to regimen type. As this study was not designed to compare individual insulin analogues, these findings should be interpreted cautiously.

In contrast to basal insulin, prandial insulin affects postprandial lipoprotein dynamics more directly. Yamada et al reported that following a standardized meal, glulisine induced a small early rise in RLP-cholesterol (+0.5 mg/dL at 30 minutes).²² This transient elevation suggests that, despite its rapid onset, glulisine still permits a brief window of increased chylomicron formation or slower early remnant clearance. Mechanistically, this underscores how the timing and intensity of prandial insulin action can shape immediate postprandial lipoprotein flux, influencing the generation of remnant particles. However, this early fluctuation does not contradict its therapeutic benefit; rather, it highlights that prandial insulin acts rapidly but requires coordinated basal support to fully suppress remnant formation throughout the postprandial period. Overall, these findings reinforce the physiological rationale for combining basal and prandial insulin.

The combination of basal insulin degludec and prandial insulin aspart simultaneously suppresses fasting and postprandial glucose, thereby reducing the availability of lipogenic substrates, inhibiting VLDL synthesis, and increasing LPL activity and reverse cholesterol transport via HDL-C.^{46–48} This dual effect contributes to reduced atherogenic RC accumulation and improved lipid profiles. Several studies also report that basal insulin detemir lowers serum triglyceride levels more effectively than glargine and can increase HDL-C levels.^{19,49,50} This advantage is often attributed to detemir's stronger effect on reducing hepatic VLDL secretion and its ability to improve peripheral insulin sensitivity, which together promote more efficient clearance of TRLs. Meanwhile, the combination of insulin degludec–aspart (IDegAsp) has been shown to lower RC and TC levels without lowering HDL-C, making it a safe and effective long-term therapy option. In real-world data, IDegAsp achieved substantial and sustained reductions in HbA1c and fasting plasma glucose despite patients' prior inadequate response to insulin therapy, indicating enhanced metabolic efficiency. Additionally, early reductions in LDL-C and TC observed after IDegAsp initiation point to a modest short-term improvement in lipid handling, which may indirectly support more favorable RC dynamics.⁵¹ Furthermore, Ryzodeg is designed to mimic physiological insulin secretion patterns by simultaneously controlling both fasting and postprandial glucose levels, thereby reducing glycemic volatility, a factor known to aggravate remnant lipoprotein accumulation and impair RC clearance pathways. Another study demonstrated a significant reduction in HbA1c levels, along with a lower incidence of hypoglycemia, compared to conventional basal–bolus regimens. The improvement in HbA1c reflects not only tighter average glycemic control but also greater day-to-day glucose stability, which reduces the likelihood of sharp glycemic swings that precipitate hypoglycemia. This dual mechanism of action supports broader metabolic effects on improving atherogenic dyslipidemia, including reduced RC levels and increased protective HDL-C.⁵²

Previous studies have confirmed that more comprehensive glycemic control is closely associated with improved lipid profiles in patients with T2DM.^{49,50} However, our study shows that the difference in the effects of insulin regimens is more pronounced in RC compared to conventional lipid profiles. Although basal insulin regimens can suppress fasting glucose and provide glycemic stability, this mechanism is insufficient to prevent the postprandial glucose spike, which is a major contributor to increased hepatic lipogenesis and the production of triglyceride-rich VLDL.^{40,41} In contrast, combined basal–prandial insulin targets both fasting and postprandial glucose, thereby reducing the availability of lipogenic substrates and accelerating the clearance of remnant particles by increasing LPL activity.^{53,54} This mechanism may help explain the descriptive differences observed between groups; however, it does not establish an independent effect of the basal–prandial regimen on RC levels within this cross-sectional analysis.

RCs, as TG-rich remnant lipoprotein particles, play a central role in atherogenesis and cardiovascular risk.^{48,55} RCs are small, readily penetrate the endothelium, and are prone to being captured by macrophages via scavenger receptors, forming foam cells that trigger vascular inflammation and atherosclerotic plaque formation. Compared with LDL-C, RCs have a longer half-life, resulting in greater atherogenic exposure to the vascular wall. In T2DM, chronic hyperglycemia further aggravates this disturbance by impairing LPL expression and activity, while simultaneously stimulating hepatic VLDL production. Persistent glucose elevation promotes insulin resistance in adipose tissue, reducing insulin's ability to activate LPL and thereby slowing the clearance of TRLs. At the same time, excess intracellular glucose enhances *de novo* lipogenesis in the

liver, increasing the secretion of VLDL particles. Together, these processes amplify the circulating pool of TRLs and their remnants, contributing to elevated RC and a more atherogenic lipid profile.^{27,30,31} In our study, descriptively lower RC levels were observed in the basal–prandial group, which is biologically consistent with these mechanisms. However, this association did not remain significant after adjustment, suggesting that factors beyond the insulin regimen play a more dominant role in determining RC levels. These findings support the theory that postprandial glucose control plays a crucial role in suppressing postprandial lipemia and improving lipoprotein metabolism, including RCs.

Furthermore, regression analysis showed that normal HDL-C levels were closely associated with achieving normal RC, regardless of the type of insulin regimens used.^{48,56} This is in line with the protective role of HDL-C in reverse cholesterol transport, which helps reduce the accumulation of atherogenic particles.^{57,58} Beyond simply acting as a cholesterol carrier, HDL facilitates the efflux of cholesterol from peripheral tissues, including lipid-laden macrophages in the arterial wall back to the liver for excretion. HDL also supports the activity of key enzymes such as Lecithin-Cholesterol Acyltransferase (LCAT) and hepatic lipase, stabilizes LPL function, and modulates inflammation and oxidative stress within the vascular environment.⁵⁹ Through these coordinated actions, higher HDL-C not only promotes cholesterol clearance but also limits the formation and persistence of remnant lipoproteins, thereby attenuating their atherogenic potential. In this context, improved glycemic control may support more favourable interactions between HDL-C and RC metabolism. However, our multivariate findings suggest that HDL-C itself, rather than insulin regimen type, is more strongly associated with RC status.^{47,60} Interestingly, although the association between insulin regimens and RC in multivariate analysis was reduced in significance, this suggests that other factors, such as duration of diabetes, BMI, and visceral fat distribution, have a strong influence in mediating the effects of insulin on lipid profiles. This attenuation further suggests that factors such as diabetes duration, adiposity, and lipid metabolism play a more dominant role in determining RC levels than insulin regimen alone.

Longer duration of T2DM has been consistently linked to progressive deterioration of lipid handling, with studies reporting higher TG, elevated VLDL, and reduced HDL-C as disease duration increases, all of which promote greater RC formation.⁶¹ Adiposity exerts an equally strong effect: individuals with higher BMI demonstrate significantly more atherogenic lipid profiles, including elevated TG and depressed HDL-C, reflecting enhanced production and delayed clearance of RC.⁶² Visceral fat appears to be particularly influential, its accumulation is known to play a major role in increasing insulin resistance and lipid metabolic dysfunction, which ultimately contribute to increased RC levels.⁶³ In a large NHANES analysis involving over 5000 adults, RC levels showed a strong, graded relationship with visceral adipose tissue, where the prevalence of visceral obesity rose from 16.5% to 74.5% across increasing RC quartiles.⁶⁴ Notably, RC remained independently associated with visceral obesity even after adjustment for major cardiometabolic confounders, and outperformed traditional lipid markers in predicting VAT burden.⁶⁴ Therefore, therapeutic interventions in T2DM patients need to focus not only on glycemic control but also on improving body composition and insulin resistance to optimize the improvement of atherogenic lipid profiles. Overall, the results of this study suggest that insulin therapy is closely linked to both glucose regulation and lipid metabolism in type 2 diabetes. However, the levels of the risk factor C-Reactive Protein appear to be more strongly influenced by factors such as HDL-C, adiposity, and diabetes duration than by the type of insulin regimen alone.

These findings have important clinical implications. Insulin selection in T2DM patients should consider not only glycemic control but also its impact on cardiovascular risk through modification of the atherogenic lipid profile. Additionally, insulin preparation may be designed to work longer or when the insulin-degrading enzyme is inhibited by modifying the structure of insulin to become more durable, while maintaining its hormone function, such as the selenoinsulin.⁶⁵

Basal insulin remains an effective initial choice, especially in patients with modest needs, low risk of hypoglycemia, or a preference for single-dose insulin. In patients with high cardiometabolic risk or predominant visceral fat accumulation, insulin regimen selection should be individualized based on overall glycemic needs, hypoglycemia risk, and patient characteristics. Although descriptively lower RC levels were observed in the basal–prandial group, the absence of an independent association indicates that regimen choice should not be based on RC considerations alone. However, given the observational and cross-sectional nature of this study, these findings should not be used to directly guide insulin regimen selection without confirmation from longitudinal or interventional studies. Therefore, these study results

strengthen the evidence that RC can be a potential biomarker for evaluating the effectiveness of insulin regimens, as well as a target for intervention to reduce the risk of atherosclerosis and cardiovascular disease in T2DM patients. Future longitudinal and interventional studies are needed to clarify whether specific insulin strategies exert direct effects on remnant lipoprotein metabolism beyond their impact on overall glycemic control.

Limitations

Several limitations should be acknowledged when interpreting these findings. First, multicentre research with a larger population is required to ensure the findings have strong external validity and can be generalized more widely. Second, this study did not include other lipid biomarkers such as VLDL, apolipoprotein B (ApoB), and apolipoprotein A1 (ApoA1), which may provide a more comprehensive illustration of the mechanisms of dyslipidemia in patients on insulin regimens. VLDL is a triglyceride-rich lipoprotein associated with insulin resistance, while ApoB reflects the number of atherogenic lipoprotein particles more accurately than LDL-C, and ApoA1 plays a role in reverse cholesterol transport. Third, the ApoB/ApoA1 ratio is known to be a strong predictor of cardiovascular risk; however, it was not evaluated in this study. Furthermore, due to the cross-sectional design of this study, the causal relationship between insulin regimen, changes in RC levels, and cardiovascular events cannot be determined. Additionally, the modest sample size may have limited statistical power and the stability of multivariable estimates. Therefore, long-term prospective studies with larger sample sizes, more diverse multicenter populations, and the inclusion of non-conventional lipid biomarkers are required to validate these findings and expand the understanding of the mechanisms underlying atherogenic dyslipidemia in patients with T2DM. Accordingly, the observed associations should be interpreted as hypothesis-generating rather than confirmatory.

Conclusion

The characteristics of T2DM patients in this study showed that those receiving insulin therapy, whether basal or combination regimens, shared similar characteristics: older age, non-obese BMI, uncontrolled blood pressure, and low HDL-C levels. RC levels were descriptively lower in patients receiving the basal–prandial combination compared to basal insulin alone. However, this association was not statistically significant after multivariable adjustment, indicating that the relationship between insulin regimen and remnant cholesterol was not independent. Given the cross-sectional design, causal inferences regarding the effect of insulin regimen on remnant cholesterol cannot be drawn. RC levels appear to reflect the combined influence of multiple metabolic factors, including lipid parameters, duration of diabetes, and adiposity, rather than a direct effect of insulin regimen alone. Consequently, the management of patients with T2DM should consider overall metabolic risk profiles in addition to glycemic control when addressing cardiovascular risk. Several important limitations should be acknowledged, including the relatively small sample size constraints related to events per variable in logistic regression, exclusion of statin users, and the absence of longitudinal follow-up. Therefore, these findings should be interpreted as hypothesis-generating rather than confirmatory. Prospective studies with larger sample sizes and longitudinal or interventional designs are required to clarify whether different insulin regimens exert a causal effect on RC and long-term cardiovascular risk in patients with T2DM.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study has been reviewed and approved by the Research Ethics Committee of Padjadjaran University with ethical approval document number 652/UN6.KEP/EC/2025 dated July 30, 2025, signed by Dr. med. Muhammad Hasan Bashari, dr., M.Kes. This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Consent to participate was signed by all participants or their family members.

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Author Contributions

Ramdhani M. Natsir: Data curation, Formal analysis, Funding acquisition, Investigation, Writing – original draft. Eli Halimah: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review and editing. Ajeng Diantini: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review and editing. Jutti Levita: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review and editing. Husaini Umar: Data curation, Methodology, Resources, Validation, Writing – original draft. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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