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Comparison of fasting and non-fasting lipid profiles in a large cohort of patients presenting at a community hospital

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Abstract

Objective: To compare the fasting and non-fasting lipid profile including ApoB in a cohort of patients from a community setting. Our purpose was to determine the proportion of results that could be explained by the known biological variation in the fasting state and to examine the additional impact of non-fasting on these same lipid parameters.

Methods: 1093 adult outpatients with fasting lipid requests were recruited from February to September 2016 at the blood collection sites of the Moncton Hospital. Participants were asked to come back in the next 3-4 days after having eaten a regular breakfast to have their blood drawn for a non-fasting lipid profile.

Results: 91.6% of patients in this study had a change in total cholesterol that fell within the biological variation expected for this parameter. Similar results were seen for HDL-C (94.3%) non-HDL-C (88.8%) and ApoB (93.0%). A smaller number of patients fell within the biological variation expected for TG (78.8%) and LDL-C (74.6%). An average TG increase of 0.3 mmol/L was observed in fed patients no matter the level of fasting TG. A gradual widening in the range of change in TG concentration was observed as fasting TG increased. Similar results were seen in diabetic patients.

Conclusion: Outside of LDL-C and TG, little changes were seen in lipid parameters in the postprandial state. A large part of these changes could be explained by the biological variation. We observed a gradual widening in the range of increase in TG for patients with higher fasting TG. Non HDL-C and ApoB should be the treatment target of choice for patients in the non-fasting state.

Keywords: lipid profile, fasting, non-fasting, biological variation, lipid target, diabetes

Introduction

It has been the standard of practice in North America to measure the lipid profile in the fasting state. A growing body of evidence (1-8) suggesting that fasting is not routinely required prior to lipid testing has led to changes in the latest guidelines. European lipid guidelines (9) now recommend that fasting should not be required for the routine determination of a lipid profile. More recently the Canadian Cardiovascular Society has also released updated lipid guidelines that advocate non-fasting routine lipid testing (10). As 30% of the population (11) and approximately 50% of diabetic patients have increased fasting TG levels it becomes important to examine more closely the effect of food intake on the lipid profile of subgroups of patients with elevated fasting TG levels. It has been documented that these patients have a longer and higher peak TG response following a fat load. (12-16). In population studies, TG is found to increase by an average of 0.3 mmol/L when compared with fasting results. This change is considered of relatively low clinical consequences. However, it should be emphasized that this value represents a mean from a high number of patients, the majority of which have values within the reference range. Since the timing and the food content of the meal is not standardized, individual responses to a ‘’non fasting state’’ may vary considerably. In many cases, the sampling might be done in a state close to fasting as after a meal like breakfast with a low fat content. In such a case, the observed changes in TG, cholesterol and other lipid parameters might only reflect known biological variations seen in the fasting state. The proportion of non-fasting results outside the expected biological variation of fasting results is important to consider if one is to establish equivalence for these parameters. Furthermore, the impact of non-fasting sampling may be different in subgroups of patients with normal, intermediate and high TG levels.

It is expected that the use of the non-fasting lipid profile will become standard practice in the short term. It is important to identify potential pitfalls and the best way to evaluate results. Some authors (17) suggest a cautious approach when measuring lipids from a non-fasting sample along with guidelines that use fixed LDL-C targets. It is well known that LDL-C is underestimated in patients with TG above 1.7 mmol/L (18). The calculated LDL-C is reported to decrease on average by 0.1-0.2 mmol/L in the non-fasting state. It would be logical to assume that the disconnect between the different lipid targets (LDL-C versus Non HDL-C and ApoB) can only worsen as TG increases following food intake (19).

Here, we report on a study comparing the fasting and non-fasting lipid profile including ApoB in a large cohort of patients from a community setting. Our purpose was to determine the proportion of lipid results that could be explained by the known biological variation and to examine the additional impact of food intake on these same parameters. These effects were evaluated in subgroups of patients with different fasting TG levels, including a group with TG above 4.5 mmol/L. We also wanted to verify the threshold at which the TG level is abnormal in the non-fasting state. Finally, we assessed the effect of non-fasting results in relation to fixed targets for LDL-C, Non-HDL-C and ApoB.

Methods

Adult outpatients with standard fasting lipid requests were recruited from February to September 2016 at the blood collection sites of the Moncton Hospital, New Brunswick, Canada. Some patients known to have high TG were also called at home to invite them to participate in the study. Participants were asked to fill a short questionnaire (demographics, medical history) and a consent form. Participants had a first fasting sampling and were asked to comeback in the next 3-4 days in the morning, after having eaten a regular breakfast, to have their blood drawn for a non-fasting lipid profile. Another smaller group of patients was recruited from a diabetes clinic of the Moncton Hospital. This project was approved by the Ethical Committee of Horizon Health Network. All chemistry parameters including lipids (total cholesterol, HDL-C, triglycerides and ApoB) were measured on an Abbott Chemistry Analyzer (Architect c 16000) while HbA1C (A1C) was measured on the Variant II from Biorad. LDL-C was derived from the Friedewald equation (20) for TG <= 4.5 mmol/L. The limit of expected biological variation, found by repeats in the fasting state, for each parameter was set at +/- 2 standard deviations of consensus values from the latest update of a public database (21, 22). The reported 2 SD biological variability are respectively: total cholesterol 11.9%, TG 39.8%, HDL-C 14.6%, LDL-C 15.6%, and Apo B 13.8%. For Non HDL-C, no data is available, so we took the same value as for ApoB (13.8%) which is also close to the mean between total cholesterol and LDL-C. Thus, without any effect of food intake, we would expect about 95 % of results to fall within those boundaries. Differences between non-fasting and fasting results were calculated and expressed in absolute terms and as percentages. We studied subgroups according to TG levels since it is the most affected parameter in the non-fasting state. Contrasts between subgroups were evaluated by Chi square test or Kruskal- Wallis test where appropriate. Box plots figures include a box corresponding to the 25^{th} and 75^{th} percentile of the distribution with vertical lines extending up to 1.5 fold the box

size. Data outside this range are identified as outliers (asterisks) or extreme outliers (circles). Medians are identified by horizontal lines.

Results

Overall 1093 patients accepted to participate in this study. Average age was 62.6 (median 64.0, range 21-86, SD 10.4) years old, 50.3% were male and 42.5 % had diabetes. The time elapsed between the fasting test and the non-fasting test was 3.2 days (SD 2.0) and on average blood collection was done 1.6 (SD 1.0) hours after the first meal of the day. 98.9% of patients performed the fasting part of the study as a first test. As shown in table 1 statistically significant difference were seen ($p<0.001$) in all the lipid parameters studied: total cholesterol (-1.7 %), HDL-C (-0.8 %), ApoB (-2.1 %) and non-HDL-C (-2.0%). More significantly TG increased by 0.28 mmol/L (17%) and LDL-C decreased by 0.16 mmol/L (-6.6%)

Table 1 and Figure 1 compare the % change (fasting versus non-fasting) as a function of the fasting value for each lipid parameter studied. This change is also compared to the biological variation for each parameter. 91.6 % of the patients in this study had a change I n total cholesterol that fell within the biological variation expected for this parameter. Similar results were seen for HDL-C (94.3%), non-HDL-C (88.8%) and ApoB (93.0%). A smaller number of patients fell within the biological variation expected for TG (78.8%) and LDL-C (74.6%).

Table 1 Lipid parameters in fasting and non-fasting patients and deviation from known expected biological variation in fasting patients.

Parameter		N	Mean(SD)	Mean difference	% difference	Biological vs actual variation (%)		
						2.5	95	2.5
Cholesterol	Fasting	1093	4.75 (1.30)	-0.09	-1.7	5.2	91.6	3.2
	Non Fasting		4.66 (1.28)					
Triglycerides	Fasting	1093	2.38 (1.51)	0.28	+17.0	1.6	78.8	19.6
	Non Fasting		2.66 (1.79)					
HDL-C	Fasting	1090	1.15 (0.34)	-0.01	-0.8	2.3	94.3	3.4
	Non Fasting		1.14 (0.34)					
LDL-C	Fasting	940	2.57 (1.08)	-0.18	-6.6	20.6	74.6	4.8
	Non Fasting		2.41 (1.04)					
Non HDL-C	Fasting	1090	3.59 (1.25)	-0.08	-2.0	7.2	88.8	3.9
	Non Fasting		3.55 (1.21)					
ApoB	Fasting	1015	0.96 (0.29)	-0.02	-2.1	4.4	93.0	2.6
	Non Fasting		0.94 (0.28)					

Significant difference in the mean ($p<0.001$) for all comparisons.

All units in mmol/L except for ApoB g/L

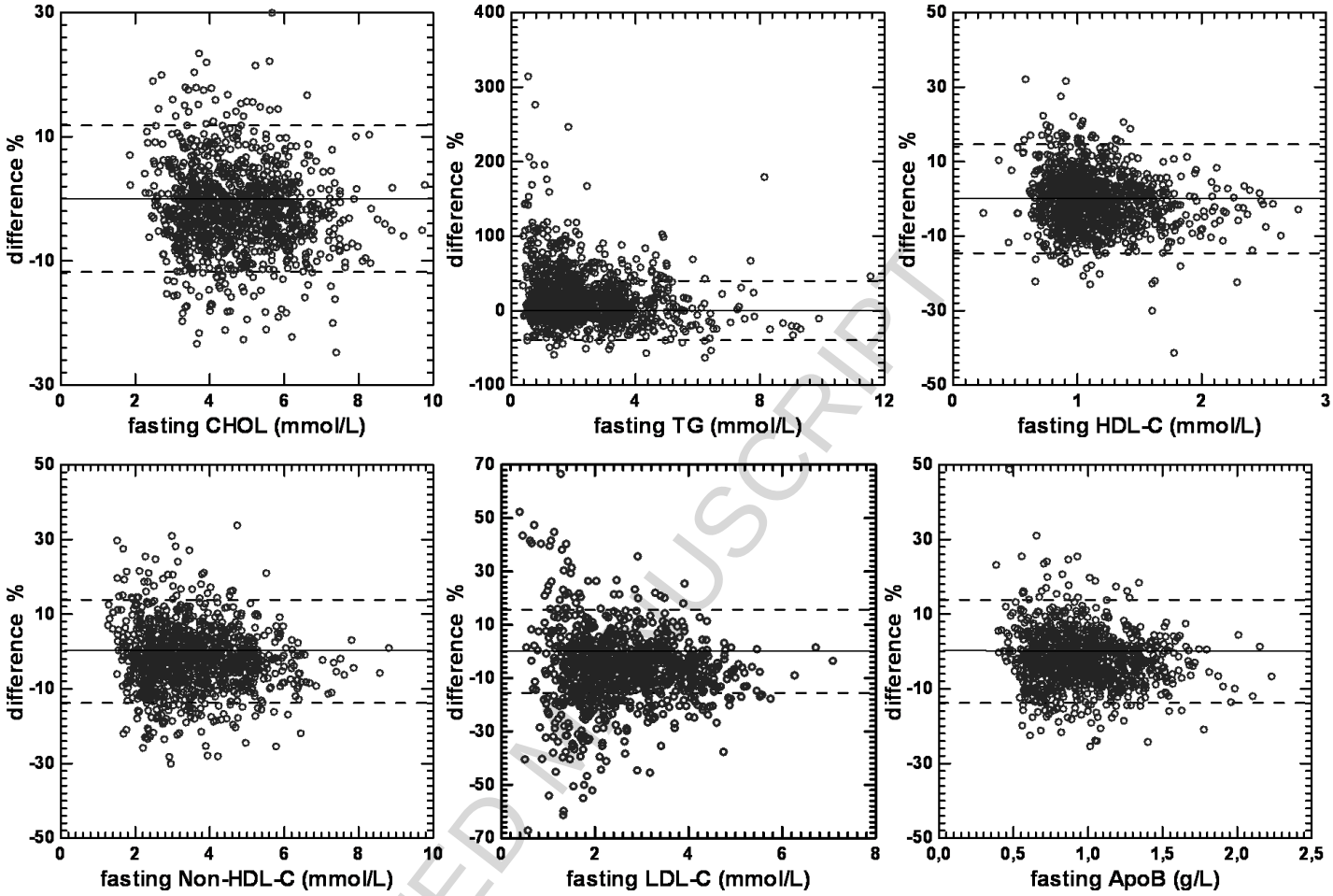

Figure 1. Comparison of the percent change (non-fasting versus fasting) in lipid parameters.

The 2 dashed lines represent the fasting biological variation (95% range)

Our study population had 38.7% of TG values below 1.7 mmol/L, 20.9% between 1.7-2.29 mmol/L and 31.0 % between 2.3-4.5 mmol/L. Finally, 9.4% of the patients studied had a fasting TG equal or above 4.5 mmol/L. When looking at the postprandial increase in TG across groups of patients with different fasting TG concentrations, we saw a mean TG increase that was relatively constant but a gradual widening in absolute terms of the range as TG increased (Table 2). In patients with normal fasting TG values the mean increase was 0.26 mmol/L (5-95 percentile: -0.31 to 1.17). Equivalent values were 0.32 mmol/L (5-95 percentile:-0.38 to1.23)

and 0.25 mmol/L (5-95 percentile: -1.0 to 1.76)) for the intermediate and high fasting TG groups. For patients with a fasting TG >= 4.5, we saw an average increase of 0.35 mmol (5-95 percentile: -2.29 to 4.0) LDL-C mean changes were – 0.17 mmol/L (-6.7%), -0.22 mmol/L (-7.8%) and - 0.16 mmol/L (-4.0%) for the normal, intermediate and high fasting TG group.

Table 2 Postprandial change in triglyceride concentration in patients grouped according to fasting triglyceride levels.

Triglyceride level in mmol/L	N	Mean Result		Difference between fasting and non-fasting results		5th percentile	95th percentile
		fasting	Non-fasting	Mean difference	% difference		
<1.70	401	1.12	1.38	0.27	24.3	-0.31	1.17
1.70-2.29	314	1.98	2.31	0.32	16.6	-0.38	1.23
2.30-4.50	337	3.2	3.45	0.25	7.90	-1	1.76
>4.50	100	5.81	6.18	0.36	6.3	-2.29	4

A linear regression comparing all 1093 patients fasting versus non-fasting predicted (Y = 0.997 +0.288) that the upper range of normal values i.e. the equivalent of 1.7 mmol/L fasting was 1.98 mmol/L in the non-fasting state. Figure 2 illustrates the capacity of a TG measurement done non-fasting to predict the range of values that can be obtained in the fasting state. For non-fasting TG concentrations below 2.0 mmol/L 81% of patients will have a fasting TG below 1.7 mmol/L. For non-fasting TG above 3.0 mmol/L 97% of patients will have a fasting TG above 1.7 mmol/L.

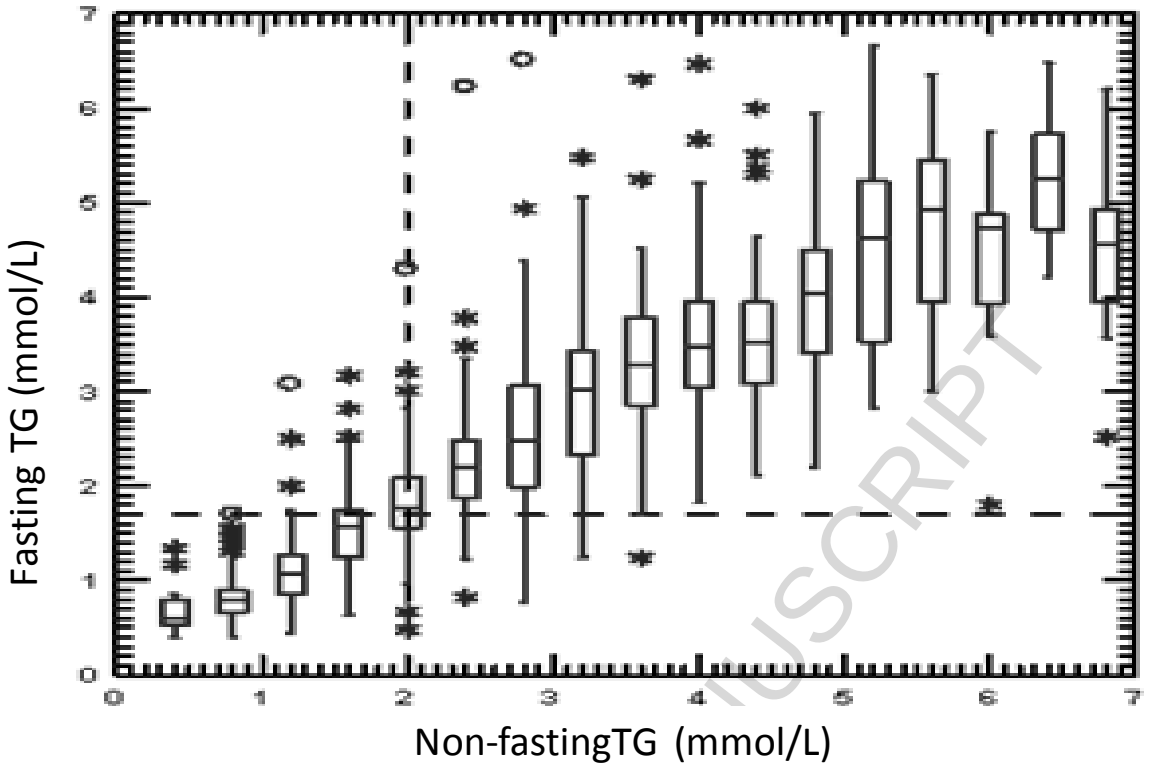

Figure 2 Distribution of fasting Triglyceride (median, 25 – 75 percentile and range) as a function of non-fasting Triglyceride.
Asterix: aberrant value circle: highly aberrant value

Figure 3 shows the % change in lipid parameters (fasting versus non-fasting) as a function of non-fasting TG concentration. We note that that there is a small negative bias in the median value for cholesterol, HDL-C, non-HDL-C and ApoB and that the 25 and 75 percentile values mostly remain with the biological variation limits. This small negative bias remains unchanged as non-fasting TG increases. For TG, we note that about 21% of patients have changes that exceed the expected known wider biological variation and that this proportion increases with increasing non- fasting TG levels. Especially interesting however, is the gradual decrease in the median value of LDL-C as non-fasting TG increases. Non-fasting samples generate a significant LDL-C bias as TG increases. For non- fasting TG higher than 2.0 mmol/L, more than 25% of cases have a negative bias that exceeds the biological variation.

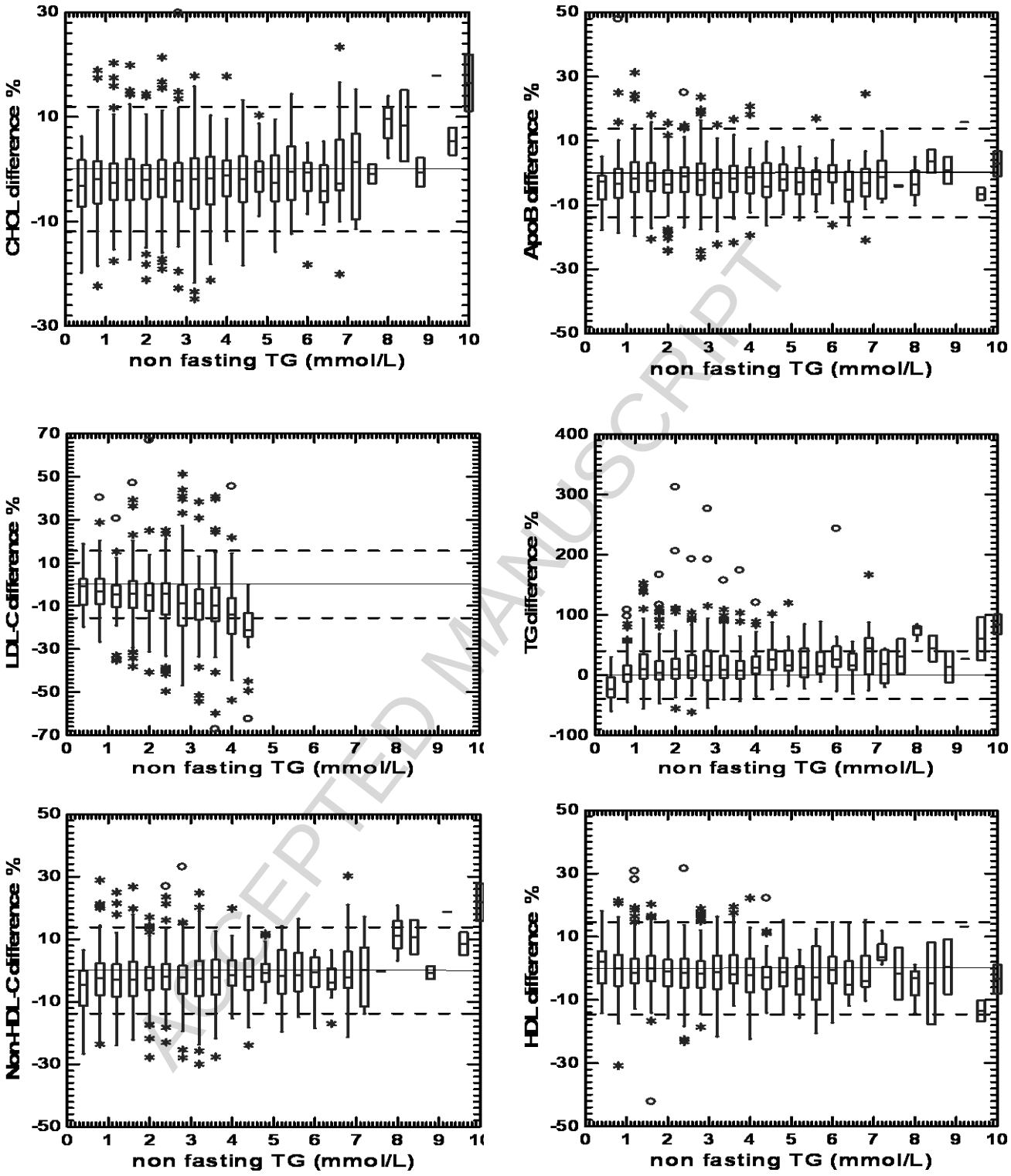

Figure 3. Percent change (median,25-75 percentile,range) in lipid parameters (fasting versus non-fasting) as a function of non-fasting triglyceride concentration.
Asterix: aberrant value circle: highly aberrant value
TG,triglyceride; Chol, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Non-HDL-C, non-high-density lipoprotein-cholesterol; ApoB, apolipoprotein B

Changes in lipid parameters following the intake of food in diabetic (mean age 63.8, range 30-83, 56% men) patients showed essentially the same pattern as for non-diabetic patients (mean age 61.8, range 21-86,46% men). Table 3 shows results for TG and LDL-C. Despite higher fasting levels of TG (2.68 mmol/L versus 2.14 mmol/L) diabetic patients experienced a similar increase in TG (0.27 mmol/L versus 0.29 mmol/L) compared to non-diabetic patients in the postprandial state. The decrease in LDL-C was also almost identical in both groups i.e. 0.17 mmol/L for diabetic patients and 0.18 mmol/L for non-diabetic patients.

Table 3 Triglyceride and LDL-C values in diabetic and non-diabetic patients measured in fasting and non-fasting samples.

		non-diabetic patients	diabetic patients	t-test probability
Parameter	N	626	467	
Triglyceride	Fasting mean (SD)	2.14 (1.39)	2.69 (1.62)	<0.001
	Non-fasting mean (SD)	2.43 (1.70)	2.96 (1.86)	<0.001
	Mean difference (SD)	+0.29 (0.96)	+0.27 (0.93)	0.73
LDL-C	Fasting mean (SD)	2.92 (1.00)	2.07 (0.98)	<0.001
	Non-fasting mean (SD)	2.74 (0.97)	1.91 (0.94)	<0.001
	Mean difference (SD)	-0.18 (0.32)	-0.17 (0.31)	0.84

All units are in mmol/L, t-test for contrasting between diabetics and non-diabetics

Discussion

Epidemiological studies have tended to conclude (1-4) that clinically non-significant differences exist between the mean of lipid parameters measured in the fasting and non-fasting state. Few studies (9,23,24) have been done using the same patient as its own control and most have only

targeted mean results. The novelty of our approach in this large cohort of patient was to use data on biological variation for each lipid parameter to get a better handle on whether or not clinically significant differences existed for a particular parameter measured fasting and non-fasting. Our data confirms that outside of TG and LDL-C comparable results are obtained in measuring the lipid profile whether the patient is fasting or not. The small decrease in total cholesterol, HDL-C, Non HDL-C and ApoB observed following the intake of food would be related to a small dilution from the fluid intake (1,3).

It has been documented (12-16) that patients with elevated fasting TG display an exaggerated and prolonged TG response when subjected to a test meal. In contrast, we observed an average increase in TG following the first meal of the day that was constant at approximately 0.3 mmol/L, no matter the level of fasting TG. Almost identical results were also found when we compared diabetic (fasting TG 2.69) to non-diabetic patients. (fasting TG 2.14 mmol/L). Many factors (dietary, physiological, genetic, pathological) are known to influence postprandial lipidemia (25) The main nutritional factor influencing postprandial lipidemia is the amount of fat present in a meal. All studies cited above used a test meal containing a very high fat content. We estimate that the fat content of a typical breakfast for the participants in our study was much lower and that is why we did not replicate these observations. (26,27). However, we did note that as fasting TG increased, the range of change in TG concentration increased substantially and became quite wide above 4.5 mmol/L. For 90% of patients with fasting TG < 4.5 mmol/L this range did not exceed - 1.00 to +1.75 mmol/L while for patients with fasting TG values above 4.5 mmol/L it covered the range of -2.29 to +4 mmol/L. This data is in agreement with previous recommendations (9, 10) suggesting to use of a fasting lipid profile with patients that have TG levels above 4.5 mmol/L

The linear regression that we performed on the TG data for all patients (fasting TG versus non-fasting) appears to confirm (9, 28) that the upper range for flagging an abnormally high TG

result is approximately 2.0 mmol/L. In the Women's Health Study (28) done on 20,118 fasting and 6391 non-fasting healthy women followed for <= 17 years, a non-fasting TG of 1.98 mmol/L identified a threshold which predicted an increased cardiovascular risk. Other studies have also shown that an elevated non-fasting TG level is associated a higher cardiovascular risk (6,31,32).

In performing a standard lipid profile, we previously have shown (19) that a discrepancy exists in the % of patients within target for LDL-C in relation to non-HDL-C and ApoB as fasting TG increases. The reasons for this discordance is related not only to underestimation (18) of the calculated LDL-C but also to the accumulation of harmful triglyceride-rich lipoproteins (TRL) and their remnants (33-34) that are not fully taken into account by the measurement of only LDL-C. An average 0.3 mmol/L increase in TG following the first meal of the day is expected to further accentuate the discordance in the % of patients within target for LDL-C in relation to non-HDL-C and ApoB. In our study, LDL-C decreased from to 2.07 in the fasting state to 1.91 mmol/L in the non-fasting state. However, some individuals may see a much bigger decrease in LDL-C as their non-fasting TG increases significantly above the average of 0.3 mmol/L. Chylomicrons, the carriers of TG in the post-prandial state, are responsible for the underestimation of calculated LDL-C by the Friedewald equation. This equation was originally derived from fasting samples. It is worth noting that this effect is seen for TG concentrations as low as 1.5-2.0 mmol/L. In other words, the validity of the Friedewald equation is doubtful for TG over 1.5 mmol/L. Over 20% of patients in our study show negative biases for LDL-C that exceeds expected biological variation. This lowering effect on LDL-C gives physicians the false assurance that patients have been adequately treated. Lipid guidelines in the past have not been forthright enough in promoting the message that LDL-C is not a valid target when TG is above normal values. Clinicians should be aware that non-fasting affects not only TG but may

cause falsely low LDL-C in a significant proportion of cases. One study (3) has reported a 0.6 mmol/L decrease in LDL-C following food intake in a diabetic population.

Authors of the Copenhagen City Heart study (31) have shown that a strong linear relationship exists between non-fasting TG concentration and the amount of remnant lipoprotein cholesterol that accumulates in blood. Those particles are thought to be strongly atherogenic. The lack of agreement in fixed lipid targets (LDL-C versus non-HDL-C and ApoB) when TG concentration is above normal is recognized in the recent Canadian lipid guidelines (10) which have recommended the use of Non HDL-C or ApoB as the target of choice when TG levels (fasting or non-fasting) are above 1.5 mmol/L. The routine use of a non-fasting lipid profile is another strong argument to favor the alternate lipid targets non- HDL-C and ApoB over LDL-C. Non fasting LDL-C is not reliable when TG exceeds 1.5 mmol/L.

Limitations of the study: Fat intake at breakfast is usually less than at other meals of the day. For this reason, we cannot conclude with certainty that the lipid parameters would change in the same manner following midday and evening meals. However, results from 2 studies on free living individuals, one done on 58 healthy normolipemic men (33) and the other one (34) on 145 type 2 diabetic patients (66 men and 79 women) and 30 controls gives us some insight into what can be expected. In the first study fasting TG was at 1.2 mmol/L and increased by 0.30 mmol/L following breakfast, 0.69 mmol/L following lunch and 1.15 mmol/L following dinner. Fat intake at breakfast was smallest at 17.6 g, 25.4 g at lunch and biggest at dinner 34.9g. This pattern of eating would resemble what is seen in our patient population. In the second study done on diabetic patients fasting TG went from a value of 2.22 to a maximum of 2.73 mmol/L (+ 0.51) following lunch. The TG values in the control group showed a similar pattern but were on average 0.73 mmol/L lower. Worth noting is that in this Italian study the biggest meal of the day is taken at midday. Since the overwhelming majority of non-fasting lipid testing is done in the morning and afternoon an average TG increases of approximately 0.3-0.6 mmol/L could be

reasonably expected. Despite the short period of time, 3.2 days on average, between the fasting and non-fasting test, it was not possible to completely control for variables (changes in medication, exercise, alcohol, dietary excesses, etc.) that could influence the results.

In summary we conclude that outside of TG and LDL-C, we see little changes in lipid parameters following the first meal of the day. A large part of the change in lipid parameters following the intake of food can be explained by the biological variation seen in the fasting state. The average increase in TG in the postprandial state was relatively constant at around 0.3 mmol/L no matter the fasting TG level. However a wider range of change in TG concentration was seen in patients as fasting TG levels increased. Because of the more extreme range of change in TG levels in patients with a fasting TG above 4.5 mmol/L we concur with previous recommendations that these patients should be tested fasting. As TG concentration increases, there is discordance in the treatment targets for LDL-C in relation to non-HDL-C and ApoB. LDL-C is an unreliable target in patients with elevated fasting TG i.e. 30% of the adult population and approximately 50% of diabetics. In this context, the increase in TG following food ingestion further invalidates this parameter as a useful tool in the follow up of dyslipidemia patients.

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Author Disclosures:

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Author Contribution

CC and ML were involved in the actual running of the project and reviewed the manuscript. LJC and PD contributed to the conception, design, analysis, interpretation of the data and drafting of the article.

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