Published in final edited form as:

Nutrition. 2012 February ; 28(2): 131–137. doi:10.1016/j.nut.2011.04.001.

Dietary intervention induces flow of changes within biomarkers of lipids, inflammation, liver enzymes, and glycemic control

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Abstract

Objective—To determine how changes in lipids, liver enzymes, and inflammatory and glycemia markers intercorrelate during prolonged dietary intervention in obese participants with or without type 2 diabetes (T2D).

Methods—We examined the dynamics and intercorrelations among changes in biomarkers during the 2-y Dietary Intervention Randomized Controlled Trial (DIRECT) in 322 participants (including 46 with T2D; 52 y of age, body mass index 31 kg/m²) throughout rapid weight loss (0–6 mo) and weight-maintenance/regain (7–24 mo) phases.

Results—The 2-y increase of high-density lipoprotein cholesterol was greater in participants with T2D (+9.41 versus +6.57 mg/dL, $P < 0.05$), although they tended to have smaller waist circumferences (−2.1 versus −4.0 cm, $P = 0.08$). In models adjusted for age, sex, and weight loss, the 2-year decrease of triacylglycerols was associated with increases of low-density and high-density lipoprotein cholesterol. An increase of apolipoprotein A1 was associated with a decrease in high-sensitive C-reactive protein ($P < 0.05$ for all comparisons). Exclusively in participants with T2D, the 2-year decrease in triacylglycerols was further correlated with decreases in apolipoprotein B100 and liver enzymes, and a decrease in fasting glucose correlated with decreases in low-density lipoprotein cholesterol, apolipoprotein B100, and alanine aminotransferase ($P < 0.05$ for all comparisons). In the entire group, multivariate models adjusted for age, sex, intervention group, and 6-mo weight loss identified decreased high-sensitive C-reactive protein at 6 mo as an exclusive predictor of a greater decrease in triacylglycerols ($\beta =$

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0.154, $P = 0.008$) and a greater increase in high-density lipoprotein cholesterol ($\beta = -0.452$, $P = 0.005$) during the subsequent 18 mo.

Conclusions—Long-term dietary intervention induces a flow of changes within biomarkers and the cross-talk is likely to be stronger in T2D. A decrease in systemic inflammation during the weight-loss phase may predict greater long-term improvement in lipids (www.ClinicalTrials.gov, identifier NCT00160108).

Keywords

Dietary intervention; Biomarkers; Weight loss; Weight maintenance; Diabetes

Introduction

Various biomarkers reflecting cardiometabolic risk, including lipid biomarkers, inflammatory parameters, liver enzymes, and metabolic parameters of insulin resistance, tend to be intercorrelated in the obese state [1,2]. Diet-induced weight loss is known to induce significant favorable effects, e.g., improving systolic and diastolic blood pressure [3], lowering low-density lipoprotein cholesterol (LDL-C) and total cholesterol, increasing high-density lipoprotein cholesterol (HDL-C) concentrations [4], and decreasing inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP) [2] and insulin sensitivity [5], resulting in a lower estimated cardiovascular risk.

Unfavorable lifestyle habits are well-accepted pathogenic factors in type 2 diabetes (T2D) and its related morbidities. Nutritional and lifestyle modifications have repeatedly been shown as effective modalities in the primary prevention of the disease [6] and in improving glycemic control [7]. Nevertheless, the actual real-life efficacy of nutritional intervention in persons with established diabetes to improve their long-term prognosis is still being questioned by practitioners. This is not only because modifying lifestyle habits such as nutrition and physical activity is difficult to maintain over time [8], but also because persons with diabetes may be resistant to certain beneficial effects of such interventions [9]. Among persons with established diabetes, low-grade inflammation has been shown to be positively related to dyslipidemia [10], and a positive correlation among serum hs-CRP, hemoglobin A1c, and fasting insulin has been reported in men with T2D regardless of the presence of coronary heart disease [11]. Although the effects of diet-induced weight loss on biomarkers are documented, how changes in one biomarker correlate with changes in other biomarkers and whether such intercorrelations differ in persons with T2D versus persons without diabetes remain poorly studied. Moreover, during dietary interventions, it is unknown whether all beneficial changes are dependent on the degree of weight loss.

In the recent 2-year Dietary Intervention Randomized Controlled Trial (DIRECT) [12] in 322 participants, which was originally designed to compare the effectiveness and safety of popular diets, we concluded that several different dietary strategies are effective for weight loss, suggesting that individualized preferences and metabolic considerations should be taken into account when prescribing dietary interventions. In the DIRECT, although the rates of adherence to the dietary intervention were 95% at 1 y and 85% at 2 y, we distinguished between a rapid weight-loss phase (0–6 mo) and the maintenance/regain phase (7–24 mo).

Because significant improvements in some biomarker levels were observed throughout the 2-y intervention, we aimed at assessing the dynamics in biomarkers, flow, and the intercorrelations among changes of fasting lipids, inflammation, liver enzymes, and glycemic control beyond the effect of weight loss. Such information may allow a better definition of clinical indications for dietary intervention and for setting realistic expectations for such interventions in obesity and diabetes.

Materials and methods

Study population and intervention

The DIRECT [12] was conducted from July 2005 through June 2007 in a research center workplace with an active on-site medical clinic. Eligible participants were men and women 40 to 65 y of age with a body mass index (BMI) higher than 27 kg/m² or the presence of T2D or coronary heart disease regardless of age or BMI. Participants were randomly assigned to one of three diets: a low-fat diet [13], a Mediterranean diet [14], or a low-carbohydrate diet [15]. Each food item provided in the self-service cafeteria in the workplace was labeled, indicating the amount of calories and the carbohydrates, fat, and saturated fat content (in grams). The labels were color-coded according to diet groups and were updated daily. Adherence to the diets was evaluated by a validated [16] food-frequency questionnaire that included 127 food items [17] and close monitoring of the study's nurse. Participants received no financial compensation or gifts for participating.

The study was approved and monitored by the human subjects committee of the Soroka University Medical Center and Ben-Gurion University. Each participant provided written informed consent at the beginning of the trial.

Follow-up measurements

The participants were weighed without shoes to the nearest 0.1 kg every month. Height was measured at baseline by a wall-mounted stadiometer, to the nearest millimeter, for the determination of baseline BMI. Waist circumference (WC), measured halfway between the costal margin and the iliac crest, and blood pressure, with the use of an automated system (Datascop Acutor 4 SOMA Technology, Bloomfield, CT, USA) after 5 min of rest, were measured every 3 mo. Blood samples were obtained by venipuncture at 08:00 after a 12-h fast at baseline and after 6, 12, and 24 mo and were stored at −80°C until the performance of assays for lipids, inflammatory biomarkers, and insulin. Levels of fasting plasma glucose and liver enzymes were measured in fresh samples. Serum level of total cholesterol, HDL-C, LDL-C, and triacylglycerol (TG) were determined enzymatically with a Wako R-30 analyzer (Wako, Neuss, Germany), with coefficients of variation of 1.3% for cholesterol and 2.1% for TG. Apolipoprotein 1 (ApoA1) and apolipoprotein B100 (ApoB100) were determined in serum by an immunoturbidimetric assay (Tina-quant 2, Roche, Mannheim, Germany) on an automated Cobas c501 analyzer (Roche). The coefficients of variation were 1.0% to 4.7% for ApoA1 and 1.1% to 3.1% for ApoB100. Plasma insulin levels were measured with the use of an enzyme immunometric assay (Immulite automated analyzer, Diagnostic Products), with a coefficient of variation of 2.5%. Plasma levels of high-molecular-weight adiponectin were measured by an enzyme-linked immunosorbent assay (AdipoGen AG Liestal,

Switzerland or Axxora, Lörrach, Germany), with a coefficient of variation of 4.8%. Plasma leptin levels were assessed by an enzyme-linked immunosorbent assay (Mediagnost, Tubingen, Germany), with a coefficient of variation of 2.4%. Plasma levels of hs-CRP were measured by an enzyme-linked immunosorbent assay (DiaMed, EuroGen, Turnhout, Belgium), with a coefficient of variation of 1.9%.

Statistical analysis

We used chi-square, grouped, and paired *t* tests to evaluate the baseline characteristics of the study population and the changes in clinical measurements and biomarkers within 2 y of dietary intervention across diabetes statuses. We calculated baseline Pearson correlations among biomarkers, adjusted for age, sex, and baseline BMI stratified by diabetes, and examined the age-, sex-, and type of diet-adjusted correlations among changes in biomarkers and clinical measurements after 2 y of intervention using variables presenting the magnitude of change () of each biomarker and clinical measurement (variable = variable after 24 mo minus variable at baseline). We then examined the correlations among changes within values of biomarkers, adjusted for age, sex, and changes in weight after 2 y, to evaluate the dynamic correlations among the changes in biomarkers. In a secondary analysis, we controlled for the assigned diet rather than changes in weight. We used multivariate linear regression models, adjusted for sex, age, assigned diet group, and 6-mo weight loss, to evaluate whether changes in biomarkers after 6 mo (rapid weight-loss phase) predict changes in biomarkers in the subsequent 18 mo (maintenance/regain phase). SPSS 15 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Of the 322 DIRECT participants, 46 had T2D (Table 1). Mean BMIs at baseline were 30.3 kg/m² for participants with T2D and 31.0 kg/m² for participants without diabetes ($P = 0.245$). Participants with T2D were older (53.4 versus 50.8 y, $P = 0.01$) and had lower levels of LDL-C and HDL-C and higher levels of TG and fasting plasma glucose compared with participants without diabetes ($P < 0.05$). Lipid-lowering therapy and the ratio of total cholesterol to HDL-C were similar between groups. At baseline (Table 2), correlations adjusted for age, sex, and baseline BMI showed expected intercorrelations within the group of lipid biomarkers in the two groups. Intriguingly, in subjects with T2D, lipid biomarkers (TG and LDL-C) correlated more strongly with inflammatory markers (hs-CRP) and fasting glucose correlated more strongly with lipids (LDL-C) and liver enzymes (alkaline phosphatase).

After 2 y of intervention (Table 1), improvements in metabolic parameters, such as significant decreases in weight (kilograms and percentage), insulin, and leptin, were similar between groups. However, in participants with T2D, an increase in HDL-C (+9.41 versus +6.57 mg/dL, $P < 0.05$ between groups) and a decrease in total cholesterol/HDL-C (−1.28 versus −0.80, $P < 0.05$) were greater, despite a trend toward a lesser decrease in WC (−2.1 versus −4.0 cm, $P = 0.08$) compared with the moderately obese group.

In participants without diabetes, age-, sex-, and diet type-adjusted intercorrelations of changes in parameters showed significant associations: 2-y decreases in WC and weight were significantly correlated with decreases in TG, ApoB100, hs-CRP, and leptin and with increases in HDL-C, ApoA1, and adiponectin after 2 y ($P < 0.05$ for all comparisons; data not shown).

We next determined intercorrelations among changes in biomarkers by adjusting for the degree of weight loss. For this, the correlation matrix included values of biomarkers adjusted for age, sex, and changes in weight (Table 3). In participants without diabetes, significant intercorrelations were observed within the group of lipid biomarkers: TG correlated negatively with LDL-C and HDL-C, whereas HDL-C and LDL-C correlated positively with each other. Increases in HDL-C and ApoA1 was further associated with a decrease in hs-CRP ($P < 0.05$ for all comparisons). Intriguingly, uniquely in participants with T2D, the 2-y decrease in TG correlated with decreases in ApoB100 and liver enzymes (alanine aminotransferase and alkaline phosphatase). A decrease in fasting glucose correlated with decreases in LDL-C, ApoB100, and alanine aminotransferase ($P < 0.05$ for all comparisons). In a secondary analysis, correlations among values of biomarkers after 2 y, adjusted for age, sex, and type of assigned diet (rather than changes in weight), showed similar results (data not shown).

To further understand the associations among changes in biomarkers during the weight loss phase and their possible influence on biomarkers during the maintenance phase, we performed multivariate models within the entire study population to identify changes of biomarkers in the first phase that could predict changes independent of other biomarkers in the second phase; hs-CRP was the likely exclusive predictor. A multivariate model, adjusted for age, sex, intervention group (assigned diet), and 6-mo changes in weight, showed that a greater decrease in hs-CRP during the weight loss phase tended to be associated with a greater decrease in fasting glucose during the subsequent 18 mo ($\beta = -0.114$, $P = 0.062$), a greater decrease in TG during the subsequent 18 mo ($\beta = 0.154$, $P = 0.008$), and an increase in HDL-C ($\beta = -0.452$, $P = 0.005$).

Discussion

In this 2-y dietary intervention study, we found that long-term dietary intervention induced a cascade of changes within biomarkers of lipids, inflammation, liver enzymes, and glycemic control, with more specific intercorrelations in participants with T2D. Our results suggest that dietary modification initiates a flow of favorable changes in biomarkers that continue as long as adherence to the diet is maintained, even during the weight-regain phase. Moreover, a decrease in systemic inflammation during the weight loss phase may predict greater improvement in TG and HDL-C during the subsequent weight-maintenance/regain phase. To the best of our knowledge, the novelty of this study is that it contributes to the existing literature a matrix representing the intercorrelated changes in biomarkers and the natural history of each biomarker over a prolonged dietary intervention.

Our study has several limitations. First, although the observed intercorrelations may contribute to clarify possible biological mechanisms, we are aware that our data represent

associations rather than causative relations and that we may be observing significant correlations just by chance. However, different parameters for the same phenotype did show significant intercorrelations: For example, TG and ApoB100 (each indicating TG-rich lipoproteins) correlated with alkaline phosphatase and alanine aminotransferase (two different liver enzymes), implying a correct rather than a spurious finding. Second, we analyzed data from a rather small group of patients with diabetes. However, although significant correlations evident only in the larger non-diabetic group may represent a higher power to detect such correlations, the significant correlations found only in patients with T2D may suggest a true differential effect that is unique to this group. Third, one might argue that the closely monitored dietary intervention that resulted in significant weight loss and changes in biomarkers makes it difficult to generalize the results to other free-living populations. Nevertheless, we suggest that similar strategies for weight loss and adherence could be applied elsewhere and the intercorrelations found among changes in biomarkers may be applicable universally. The strengths of the study include the relatively long duration of the study with tight follow-up and high rate of adherence, a relatively large overall study group, and the various biomarkers analyzed.

In this study, changes in ApoA1, the apolipoprotein attached to HDL-C particles, which represents the number of HDL-C particles present in plasma, and HDL-C were associated with a decrease in levels of hs-CRP in subjects without diabetes after 2 y. Of interest, the decrease in levels of hs-CRP during the first 6 mo of intervention predicted a continued improvement in lipid profile in the maintenance/regain phase. Although an inverse correlation between hs-CRP and HDL-C has been demonstrated previously in a 1-y lifestyle intervention trial in patients with T2D [18], a cause-and-effect relation between the two could not be elucidated. One potential explanation for the prediction of HDL-C levels by hs-CRP is the key role inflammation might play in the pathogenesis of T2D [19] and cardiovascular disease and in mediating changes in other risk factors. More specifically, our results may also suggest that HDL-C is merely a reflection of the inflammatory state rather than a direct independent mediator of cardiovascular risk. Thus, after weight loss and a decreased inflammatory burden (as evident by a decrease in hs-CRP), a concomitant increase in HDL-C is observed. In support of this potential relation are results obtained from pharmacologic interventions with rosiglitazone that led to a decrease in hs-CRP and an increase in HDL-C [20,21]. Unfortunately, despite this effect of rosiglitazone, similar to the effects of torcetrapib, another pharmacologic agent that increases HDL-C and decreases CRP [22], the overall effect of cardiovascular endpoints was dismal [23]. Thus, the diet, rather than pharmacologic agents, that induced decreases in hs-CRP levels during the weight loss phase may lead to an increase in HDL-C and a decrease in cardiovascular risk in obese participants.

Notably, we found that the decrease in TG was “at the expense” of increased LDL-C and increased HDL-C. A decrease in plasma TG may occur when very LDL is converted into intermediate-density lipoprotein, which is then converted to LDL-C and results in an increase in plasma LDL-C. This phenomenon, which is especially common with pharmacologic treatments to lower TG, such as fibrates [24], might explain this negative correlation. Although there were differential effects of dietary strategies on changes of biomarkers, especially lipids and glycemic control [13], our findings showed similar results

of intercorrelations after adjustment for the type of diet or the weight loss per se, suggesting universal mechanism of this flow.

Persons with T2D are characterized by an impaired metabolic state and therefore may be more sensitive to changes in metabolic biomarkers as a result of a weight loss program. Furthermore, the degree of weight loss in response to dietary interventions may be smaller in patients with T2D than in obese participants, which has been attributed to antidiabetic therapies (that might cause weight retention such as insulin, thiazolidinediones [TZDs], and sulfonylureas) [9], lower metabolic rate [10], and/or concurrent health conditions that limit physical exercise (neuropathy and heart disease). Nevertheless, despite a relatively small group of subjects with diabetes in our study and although participants with diabetes had a smaller decrease in WC, we identified unique intercorrelations that are specific for patients with T2D. We believe this observation emphasizes the potential important benefits persons with diabetes may gain by adhering to dietary regimens irrespective of the degree of weight loss. This includes a decrease in fasting glucose, which was associated with decreases in LDL-C and liver enzymes and a decrease in TG levels, also associated with a decrease in liver enzymes. This observation may be relevant for other patients who, because of illness and specific medications, have decreased abdominal adiposity [25] but still may benefit from adhering to a nutritional intervention and improving metabolic markers.

Previous studies have suggested that an increase in alanine aminotransferase is associated with insulin resistance, impaired fasting glucose, and an increased risk for developing diabetes [26,27] and has been described as an independent predictor for developing T2D independent of insulin sensitivity, inflammatory markers, and the degree of obesity [28]. The improvement in alanine aminotransferase and fasting insulin levels after 2 y in obese participants without diabetes and the significant correlation between changes in these two parameters after 2 y may imply a lower risk for developing future diabetes and are therefore consistent with previous data.

Conclusions

Overweight persons and those with T2D in particular may greatly benefit from a structured monitored dietary intervention beyond the effect of weight loss per se. Intercorrelations can be documented among markers of inflammation, hepatic steatosis, glucose homeostasis, and lipid profile, thus affecting most components of the metabolic syndrome and its associated increased risk for cardiovascular diseases.

Acknowledgments

The authors thank the 322 participants in the DIRECT for their consistent cooperation. They thank Dr. Meir J Stampfer (Harvard School of Public Health, Boston, MA, USA), Dr. Assaf Rudich (Ben Gurion University of the Negev, Beer-Sheva, Israel), and Dr. Yaakov Henkin (Soroka University Medical Center, Beer-Sheva, Israel) for their valuable contributions.

This study was supported by the Israeli Ministry of Health, Chief Scientist Office (grants received by Drs. Shai, Schwarzfuchs, and Tirosh), a DFG grant (KFO 152, grants received by Drs. Blüher and Stumvoll), and the Dr. Robert C. and Veronica Atkins Research Foundation.

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Table 1
Baseline characteristics of study population and changes in clinical measurements and biomarkers within 2 y of dietary intervention across diabetes statuses*

Characteristic	Baseline		Change after 2 y		P between groups
	Type 2 diabetes (n = 46)	Without diabetes (n = 277)	Type 2 diabetes	Without diabetes	
Age (y)	53.4 ± 6.4 [†]	50.8 ± 6.3			
Men	42 (91.3%)	235 (85.1%)			
Current smoker	7 (15.2%)	44.0 (15.9%)			
Weight (kg)	87.9 ± 12.7 [†]	91.9 ± 13.4	-3.49 ± 5.3 [§]	-4.10 ± 5.7 [§]	0.503
BMI (kg/m ²)	30.3 ± 4.1	31.0 ± 3.5	-1.20 ± 1.7	-1.38 ± 1.9	0.559
Waist circumference (cm)	105.0 ± 10.0	106.5 ± 10.4	-2.13 ± 5.2 [§]	-3.98 ± 6.8 [§]	0.080
BP systolic (mmHg)	133.4 ± 15.6	130.4 ± 14.3	-3.06 ± 13.5	-4.26 ± 13.1 [§]	0.570
BP diastolic (mmHg)	78.0 ± 8.8	79.6 ± 9.2	-0.50 ± 9.1	-1.13 ± 8.7 [§]	0.650
Lipid-lowering therapy (%)	10 (22.5%)	61 (21.7%)			0.914
Blood biomarkers					
Serum LDL cholesterol (mg/dL)	98.6 ± 36.20 [‡]	122.5 ± 33.38	-1.59 ± 24.8	-2.98 ± 29.1	0.789
Serum HDL cholesterol (mg/dL)	34.79 ± 8.12 [†]	39.1 ± 9.29	9.41 ± 10.4 ^{†,}	6.57 ± 7.3 [§]	0.048
Serum triacylglycerol (mg/dL)	203.0 ± 99.22 [†]	165.1 ± 83.6	-29.88 ± 105.8	-13.3 ± 71.7 [§]	0.379
Total cholesterol (mg/dL)	200.99 ± 35.41 [‡]	181.52 ± 41.35	-4.23 ± 35.6	-3.14 ± 29.8	0.846
Ratio of total cholesterol to HDL cholesterol	5.4 ± 1.54	5.4 ± 1.70	-1.28 ± 1.4	-0.80 ± 1.0	0.022
Apolipoprotein A1 (mg/dL)	1.33 ± 0.23	1.37 ± 0.20	0.12 ± 0.1 [§]	0.09 ± 0.1 [§]	0.266
Apolipoprotein B100 (mg/dL)	0.78 ± 0.21 [†]	0.85 ± 0.18	0 ± 0.1	0.02 ± 0.1 [§]	0.392
Plasma high-sensitivity C-reactive protein (mg/L)	5.0 ± 3.4	4.1 ± 3.2	-0.66 ± 3.0	-0.91 ± 2.5 [§]	0.609
Plasma leptin (mg/dL)					
Men	7.8 ± 4.4	9.9 ± 6.2	-1.1 ± 2.8	-2.2 ± 3.9	0.119
Women	28.9 ± 12.8 [†]	31.2 ± 14.1	-6.3 ± 6.8	-4.6 ± 11.8	0.806
Plasma high-molecular-weight adiponectin (mg/dL)					
Men	6.0 ± 1.8	7.2 ± 2.7	0.5 ± 1.9	1.1 ± 2.5	0.214

Characteristic	Baseline		Change after 2 y		P between groups
	Type 2 diabetes (n = 46)	Without diabetes (n = 277)	Type 2 diabetes	Without diabetes	
Women	7.3 ± 3.9 [‡]	9.5 ± 3.3	1.5 ± 2.5	0.03 ± 2.5	0.340
Plasma alkaline phosphatase (U/L)	71.3 ± 23.7	72.6 ± 17.6	1.46 ± 18.9	0.096 ± 10.3	0.519
Plasma alanine aminotransferase (U/L)	27.5 ± 10.2	28.2 ± 13.0	-3.36 ± 11.1	-2.50 [§] ± 10.7	0.661
Fasting plasma insulin (μU/mL)	14.2 ± 10.05	13.9 ± 8.17	-2.63 [§] ± 5.4	-2.25 [§] ± 7.9	0.781
Fasting plasma glucose (mg/dL)	142.8 ± 53.08 [‡]	82.6 ± 12.98	-7.72 ± 53.1	2.51 [§] ± 10.9	0.257

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein

*Values are presented as mean ± SD or number of subjects (percentage). To convert values for cholesterol to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551.

[‡] P < 0.05.

[‡] P < 0.001 between groups at baseline.

[§] Within group after 2 y of intervention.

// Between groups after 2 y of intervention.

Table 2
Baseline intercorrelations among biomarkers, adjusted for age, sex, and baseline body mass index, stratified by diabetes status

	Lipoproteins				Inflammatory			Liver function			Glycemic control	
	TG	LDL-C	HDL-C	ApoB100	ApoA1	hs-CRP	Leptin	HMW adiponectin	Alkaline phosphatase	Alanine transaminase	Bilirubin	Fasting insulin
Lipoproteins												
LDL-C	-0.182 ^{*,§}											
	-0.031 [§]											
HDL-C	-0.427 [†]	0.206 ^{*,§}										
	-0.438 [*]	0.083 [§]										
ApoA1	0.221 [†]	0.867 [†]										
	0.348 [*]	0.858 [†]	NS									
ApoB100	NS	0.192 ^{*,§}	826 [†]	NS								
		0.063 [§]	0.679 [†]									
Inflammatory												
hs-CRP	0.034 [†]	0.026 [†]		0.059 [†]								
	0.389 ^{*,†}	0.445 ^{*,†}	NS	0.620 ^{†,†}	NS							
Leptin	NS	NS	-0.047 [†]	NS	-0.022 [†]	0.243 ^{*,§}						
			0.351 ^{*,†}		0.356 ^{*,†}	0.221 [§]						
HMW adiponectin	-0.135 ^{*,§}	0.174 ^{*,§}	0.300 [†]		0.249 ^{†,*}	-135 ^{*,§}	0.025 [†]					
	-0.230 [§]	-0.136 [§]	0.420 [*]	NS	0.174 [§]	-0.076 [§]	0.357 ^{*,†}					
Liver function												
Alkaline phosphatase	0.133 [*]	0.009 [†]	NS	0.047 [†]	NS	0.225 ^{†,†}	0.179 ^{*,†}	NS				
	0.355 [*]	0.404 ^{*,†}		0.377 ^{*,†}		0.236 [†]	0.280 [†]					
Alanine aminotransferase	0.206 ^{*,§}			0.155 ^{*,§}								
	0.055 [§]	NS	NS	0.219 [§]	NS	NS	NS	NS	NS			
Bilirubin	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
Glycemic control												
Fasting insulin	0.135 ^{*,§}	NS	-0.156 ^{*,§}	NS	-0.135 ^{*,§}	-0.061 [†]	0.199 ^{*,§}	-0.138 ^{*,§}	NS			0.158 [*]

Not available in PMC 2016 July 20.

	Lipoproteins				Inflammatory			Liver function			Glycemic control	
	TG	LDL-C	HDL-C	ApoB100	ApoA1	hs-CRP	Leptin	HMW adiponectin	Alkaline phosphatase	Alanine transaminase	Bilirubin	Fasting insulin
Fasting glucose	0.195 [§]	-0.015 [‡]	-0.092 [§]	-0.020 [‡]	-0.006 [§]	0.369 ^{*‡}	0.250 [§]	-0.202 [§]	-0.060 [‡]	0.373 [*]	0.030 [‡]	0.208 ^{*§}
	NS	0.505 ^{*‡}	NS	-0.020 [‡]	NS	NS	0.033 [‡]	NS	0.420 ^{*‡}	NS	0.343 ^{*‡}	0.010 [§]

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; HMW, high-molecular-weight; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerols In each cell, Pearson correlation coefficients (r) are presented for subjects without diabetes and *subjects with type 2 diabetes*.

^{*} $P < 0.05$.

[‡] $P < 0.001$.

[§] Significant ($P < 0.05$) correlations only within the diabetes group.

[§] Significant ($P < 0.05$) correlations only with the non-diabetes group.

Table 3
Intercorrelations among 2-y dietary induced changes of lipids, inflammatory biomarkers, liver enzymes, and glycemic control, stratified by diabetes status, adjusted for age, sex, and change in body mass index after 2 y

	Lipoproteins				Inflammatory			Liver function				Glycemic control	
	TG	LDL-C	HDL-C	ApoB100	ApoA1	hs-CRP	Leptin	HMW adiponectin	Alkaline phosphatase	Alanine transaminase	Bilirubin	Fasting insulin	
Lipoproteins													
LDL-C	-0.317 ^{†,‡}												
	0.103 [‡]												
HDL-C	-0.405 ^{†,‡}	0.356 ^{†,‡}											
	-0.270 [‡]	0.304 [‡]											
ApoA1	NS	NS	0.445 [‡]										
			0.590 [‡]										
ApoB100	0.050 [§]	742 [‡]											
	0.466 ^{*,§}	0.765 [‡]	NS	NS									
Inflammatory													
hs-CRP	NS	NS	-0.265 ^{*,‡}	-0.232 ^{*,‡}	NS								
			-0.322 [‡]	-0.061 [‡]									
Leptin	NS	NS	NS	NS	NS								
HMW adiponectin	NS	NS	NS	NS	NS	NS							
Liver function													
Alkaline phosphatase	0.043 [§]	NS	NS	NS	0.021 [§]	0.284 [‡]	NS	NS					
	0.605 ^{†,§}				0.471 ^{*,§}	0.399 [*]							
Alanine transaminase	-0.138 [§]	NS	0.153 ^{*,‡}	NS	-0.017 [§]	NS	NS	NS	NS				
	0.395 ^{*,§}		0.055 [‡]		0.395 ^{*,§}								
Bilirubin	NS	NS	NS	NS	NS	NS	-0.187 ^{*,‡}	-0.196 ^{*,‡}	NS	0.193 ^{*,‡}			
							0.131 [‡]	0.025 [‡]		0.336 [‡]			
Glycemic control													
Fasting insulin	0.108 [§]	NS	NS	NS	NS	NS	0.339 ^{†,‡}	NS	NS	0.158 ^{*,‡}	NS		

Nutrition. Author manuscript; available in PMC 2016 June 07.

	Lipoproteins				Inflammatory			Liver function			Glycemic control	
	TG	LDL-C	HDL-C	ApoB100	ApoA1	hs-CRP	Leptin	HMW adiponectin	Alkaline phosphatase	Alanine transaminase	Bilirubin	Fasting insulin
Fasting glucose	0.404 ^{*,§}						0.151 [‡]			0.127 [‡]		
		-0.088 [§]			-0.123 [§]					0.122 [§]		0.408 ^{‡,‡}
	NS	0.491 ^{*,§}	NS	NS	0.628 ^{‡,§}	NS	NS	NS	NS	0.523 ^{*,§}	NS	0.135 [‡]

Apo, apolipoprotein; D, magnitude of change; HDL-C, high-density lipoprotein cholesterol; HMW, high-molecular-weight; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerols

In each cell, Pearson correlation coefficients (r) are presented for subjects without diabetes and subjects with type 2 diabetes.

^{*} $P < 0.05$.

[‡] $P < 0.001$.

[‡] Significant ($P < 0.05$) correlations only within the diabetes group.

[§] Significant ($P < 0.05$) correlations only within the non-diabetes group.