

Unsaturation index and type 2 diabetes: Unknown, unloved

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suggests that UI should feature prominently on the research agenda.

Key words: Type 2 diabetes; Unsaturation index; Phospholipid; Cell membrane; Fatty acid

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Core tip: A useful parameter for interpreting analyses of membrane fatty-acid composition is the unsaturation index (UI), a measure of unsaturation that is calculated as the mean number of *cis* double bonds per fatty-acid residue multiplied by 100. The UI is a fundamental parameter that contains information about many membrane biophysical properties and behaviour. UI is a crucial index for type 2 diabetes (T2D) and other disorders, yet it is not properly considered in the scientific community. The goal of the present editorial is to familiarize the scientific T2D community with the UI.

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Abstract

A useful parameter for interpreting analyses of membrane fatty-acid composition is the unsaturation index (UI), a measure of unsaturation that is calculated as the mean number of *cis* double bonds per fatty-acid residue multiplied by 100. The UI is a fundamental parameter that contains information about many membrane biophysical properties and behavior. UI is a crucial index for type 2 diabetes (T2D) and other disorders, yet it is not properly considered in the scientific community. The goal of the present editorial is to familiarize the scientific T2D community with the UI. The idea of early systemic cell-membrane disease necessitates new thinking and

INTRODUCTION

A useful parameter for interpreting analyses of membrane fatty-acid composition is the unsaturation index (UI), a measure of unsaturation that is calculated as the mean number of *cis* double bonds per fatty-acid residue multiplied by 100^[1]. This parameter characterizes a phospholipid bilayer and describes the fluidity, or flexibility, of a biological membrane. As the UI increases, so does the distance between plasma-membrane fatty-acyl chains, decreasing their mutual attraction energy and thus increasing membrane flexibility, which promotes an increase in the number of all functional Class I glucose transporters per

Table 1 Unsaturation index of erythrocyte membrane fatty-acid composition of controls and type 2 diabetes patients without diabetic retinopathy

Fatty acids	Controls (n = 18)		T2D patients without diabetic retinopathy (n = 14)	
	% of total fatty acids ¹		% of total fatty acids ¹	
	× number of double bonds		× number of double bonds	
C14:0	0.43	-	0.48	-
C15:0	0.17	-	0.22	-
C16:0	22.41	-	23.75	-
C17:0	0.38	-	0.44	-
C18:0	17.22	-	17.72	-
C20:0	0.15	-	0.18	-
C22:0	0.33	-	0.42	-
C24:0	0.74	-	0.78	-
C16:1	0.73	0.73	1.03	1.03
C18:1 (trans)	0.22	-	0.2	-
C18:1	17.16	17.16	19.15	19.15
C20:1 n-9	0.21	0.21	0.26	0.26
C20:3 n-9	0.19	0.57	0.2	0.6
C22:1 n-9	0.06	0.06	0.09	0.09
C24:1 n-9	0.69	0.69	1.15	1.15
C18:2 n-6	12.87	25.74	10.58	21.16
C18:3 n-6	0.09	0.27	0.12	0.36
C20:2 n-6	0.2	0.4	0.23	0.46
C20:3 n-6	1.3	3.9	1.5	4.5
C20:4 n-6	13.04	52.16	11.33	45.32
C22:4 n-6	2.0	8	2.01	8.04
C22:5 n-6	0.35	1.75	0.3	1.5
C18:3 n-3	0.22	0.66	0.21	0.63
C20:5 n-3	0.97	4.85	1.03	5.15
C22:5 n-3	2.23	11.15	1.56	7.8
C22:6 n-3	4.51	27.06	2.85	17.1
Unsaturation index ²	155.36		134.3	

¹Data published by Koehrer *et al*^[5], ²The unsaturation index was calculated as the mean number of double bonds per fatty acid residue multiplied by 100.

membrane surface area^[2]. At the most basic level, the basal metabolic rate of a cell is directly linked to its cell membrane acyl composition, and thus to its UI^[3]. To date, this relationship has not received due attention in the treatment for type 2 diabetes (T2D).

The UI is a fundamental parameter that contains information about many membrane biophysical properties and behavior. Arachidonic acid and docosahexaenoic acid are key fatty acids; a minimal increase in the percentage of arachidonic acid in phospholipid tails improves membrane flexibility due to its four double bonds. A similar effect is seen for docosahexaenoic acid, with its six unsaturated bonds. UI is a crucial index for T2D and other disorders, yet it is not properly considered in the scientific community^[4]. The goal of the present editorial is to familiarize the scientific T2D community with the UI.

In the September issue of *PLoS ONE*, Koehrer *et al*^[5] reported the erythrocyte phospholipid and polyunsaturated fatty-acid composition in diabetic retinopathy. Several points in this article require additional clarification. Given that the study consisted nearly exclusively T2D patients, the reported observations are

likely to be restricted to this type of diabetes. In contrast to one previous publication, Koehrer *et al*^[5] presented measurements of total phospholipids from red blood cells, with fatty-acid composition specified for a total of 26 fatty acids. Based on the presented data, we calculated the UIs of membrane phospholipids from control subjects, T2D patients with and without retinopathy, and patients with gestational diabetes mellitus^[6]. For example, Table 1 describes the calculation of the UIs for controls and T2D patients without retinopathy included in the study of Koehrer *et al*^[5].

The UIs based on the erythrocyte membrane fatty-acid compositions reported in these studies^[5,6] yielded novel information (Table 2). First, although phosphatidylcholine and phosphatidylethanolamine comprise about 60% of the total phospholipid in the bilayer membrane of human erythrocytes, the red cell phosphatidylcholine and phosphatidylethanolamine UI of subjects with normal glucose tolerance in the gestational diabetes mellitus study^[6] are in line with the total phospholipid UI of the reference population in the diabetic retinopathy study^[5] (162.8 and 155.4, respectively; $\Delta = 4.5\%$). Second, the decrease in the UI of phosphatidylcholine and phosphatidylethanolamine for gestational diabetes mellitus patients relative to controls was substantially higher than the total phospholipid UI decrease for T2D individuals without diabetic retinopathy compared with controls (16.3% and 13.5%, respectively; $\Delta = 17.2\%$), due to two underlying phenomena, *i.e.*, a temporary gestational and a chronic prediabetic increase in plasma FFA^[7]. Third, the total phospholipid UI was substantially lower in T2D individuals than in healthy controls (134.3 and 155.4, respectively; $\Delta = 13.5\%$). Finally, the mean total phospholipid UI was substantially lower in T2D individuals with mild, moderate, and severe diabetic retinopathy than in T2D individuals without diabetic retinopathy (123.4 and 134.3, respectively; $\Delta = 8.1\%$). These experimental outcomes indicate that membrane flexibility plays an important role in microvascular complications of T2D. Further, these data support our working hypothesis: a gradual elevation of the plasma levels of saturated and monounsaturated free fatty acids causes a decrease in the number of polyunsaturated fatty-acyl chains in membrane phospholipids^[2], a classical principle of membrane biogenesis^[3,8]. In this context, it is noteworthy that our working hypothesis predicts that the transition from a healthy condition to a state with T2D will be matched by a decrease in UI, as will the transition from T2D without diabetic retinopathy to T2D with retinopathy^[2].

In a study of the relationship between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids, Borkman *et al*^[9] concluded that reduced levels of unsaturated fatty acids in the membrane may be due to a net reduction in the action of insulin, as a consequence of either insulin resistance or insulin deficiency or, alternatively, as a consequence

Table 2 Calculated unsaturation indices based on erythrocyte fatty-acid compositions reported by several studies

Disease	Participants (n)		Erythrocyte membrane	Unsaturation index ¹		Decrease (%)	Ref.
	Controls	Disease		Controls	Diabetic subjects		
T2D/T1D	18	13/1	Total phospholipid	155.4	134.3	13.5	[5]
T2D/T1D + mild DR	18	11/1	Total phospholipid	155.4	125.9	19.0	[5]
T2D/T1D + moderate DR	18	11/1	Total phospholipid	155.4	119.5	23.1	[5]
T2D/T1D + severe DR	18	19/3	Total phospholipid	155.4	124.7	19.7	[5]
T2D/T1D + proliferative DR	18	17/7	Total phospholipid	155.4	136.9	11.9	[5]
Gestational diabetes	61	53	PC + PE	162.8	137.1	16.3	[6]

¹The unsaturation index was calculated as the mean number of double bonds per fatty acid residue multiplied by 100^[4]. DR: Diabetic retinopathy; PC: Phosphatidylcholine; PE: Phosphatidylethanolamine.

of hyperinsulinaemia. This interpretation seems unlikely for the following reasons: first, gestational diabetes mellitus is a marker of a prediabetic phase characterized by time-dependent increase in insulin levels^[10,11], where the T2D phase is marked by a time-dependent decrease in insulin levels^[11]. Second, we demonstrated that patients in both phases were associated with lower UIs than were healthy controls, which suggests that insulin levels do not have an important causative role in lowering the UI. We hypothesize that a gradual increase in plasma free fatty-acid concentration during the prediabetic phase and after overt T2D^[12,13] decreases the UI^[7].

A well-known characteristic of the euglycaemic hyperinsulinaemic clamp is its wide inter-subject variability in insulin sensitivity. In a study of metabolic effects of lacidipine: a placebo-controlled study using the euglycaemic hyperinsulinaemic clamp, Morris *et al*^[14] reported that even amongst non-diabetic subjects who were homogeneous for age, sex and body weight there was a wide inter-subject variability in insulin sensitivity, *i.e.*, 5.6-16.2 mg/kg per minute where the intra-subject variability in insulin sensitivity on the two placebo study days was 9%. Since physical activity and caloric intake are individual entities, which significantly affect a persons' free fatty acid concentration, we suggest that the wide inter-subject variability may be attributable to the inter-subject variability in free fatty acid concentration, and thus in the individual UI^[13].

Despite extensive guidelines for managing T2D, in the United States during the years 2005-2008, 28.5% of adults with diabetes aged 40 years or older had diabetic retinopathy and 4.4% had advanced diabetic retinopathy^[15]. These incidences are probably due to a longstanding period of decreased UI, increasing the stiffness of both the erythrocyte and plasma membranes and, as a consequence, decreasing microcirculatory flow, ultimately leading to chronic tissue hypoxia, insufficient tissue nutrition, and diabetes-specific microvascular pathology^[2]. Thus, the idea of early systemic cell-membrane disease necessitates new thinking and suggests that UI should feature prominently on the research agenda.

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