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FEMORAL SUBCUTANEOUS LMNA (LAMIN A/C) GENE EXPRESSION CORRELATES WITH VISCERAL AND HEPATIC ADIPOSITY AND CIRCULATING INTERLEUKIN-6 IN ASIAN INDIAN TYPE 2 DIABETES MELLITUS: A CASE-CONTROL CORRELATION STUDY

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ABSTRACT

LMNA-encoded lamin A/C proteins restrain adipogenic differentiation by sequestering SREBP1 and C/EBPα at the nuclear periphery, and lamin A/C in macrophages independently drives NF-κB-mediated transcription of interleukin-6 (IL-6) and other pro-inflammatory genes; whether femoral (thigh) subcutaneous LMNA expression, a depot not previously distinguished by diabetes status at the group level in Asian Indians, nonetheless tracks systemic adiposity, ectopic fat, and the circulating inflammatory profile has not been examined. In this case-control study of 40 Asian Indian patients with type 2 diabetes mellitus (T2DM) and 40 non-diabetic controls undergoing femur surgery at a tertiary care centre in Jaipur, India, absolute LMNA expression was measured by quantitative RT-PCR in femoral subcutaneous adipose tissue, and Pearson correlation coefficients were calculated between LMNA expression and anthropometric, lipid, glycaemic, adipocytokine, DEXA-derived body-composition, and MRI-derived abdominal and hepatic fat parameters, separately within the diabetic and non-diabetic groups. In diabetics, LMNA expression correlated strongly and positively with circulating IL-6 ($r=0.80$) and negatively with MRI-derived abdominal visceral fat ($r=-0.64$) and subcutaneous fat ($r=-0.67$); no anthropometric, lipid, or glycaemic correlation reached significance. In non-diabetics, LMNA correlated positively with hepatic fat ($r=0.89$), trunk-to-limb fat mass ratio ($r=0.70$), HDL-C ($r=0.62$), VLDL-C ($r=0.49$), TNF-α ($r=0.41$), triglycerides ($r=0.33$), and the trunk:leg fat ratio ($r=0.32$), and negatively with total body fat percentage ($r=-0.29$) and fat mass/height² ($r=-0.25$). The relationship between peripheral LMNA expression and the metabolic phenotype thus appears reorganised, rather than simply absent, in T2DM: the physiological coupling with adiposity and lipid handling seen in non-diabetics is lost, and a disease-specific coupling with circulating IL-6 emerges. These hypothesis-generating findings, from a previously unreported correlation analysis of an existing cohort, warrant replication with per-subject macrophage phenotyping and protein-level validation.

KEYWORDS: LMNA; Lamin A/C; Interleukin-6; Adipose tissue; Type 2 diabetes mellitus; Asian Indians

INTRODUCTION

India is home to one of the world's largest diabetic populations, and Asian Indians characteristically develop type 2 diabetes mellitus (T2DM) at a younger age and lower body mass index (BMI) than European populations (Anjana et al., 2017; Gujral et al., 2013). This susceptibility has been attributed to a distinct "thin-fat" phenotype, in which a comparatively low body weight conceals disproportionate central and visceral adiposity, a constitutionally limited subcutaneous storage compartment, and heightened insulin resistance (Yajnik et al., 2003; Sniderman et al., 2007). The adipose tissue expandability hypothesis, and the related concept of adiposopathy, propose that once the subcutaneous compartment reaches its storage ceiling, surplus lipid is diverted into visceral and ectopic depots such as the liver, where it drives insulin resistance more directly than fat mass itself (Virtue and Vidal-Puig, 2010; Bays, 2011).

LMNA encodes the A-type nuclear lamins, lamin A and lamin C, intermediate filament proteins that line the inner nuclear membrane and organise peripheral chromatin. Beyond this structural role, lamin A/C binds and sequesters sterol regulatory element-binding protein 1 (SREBP1) and CCAAT/enhancer-binding protein alpha (C/EBPα) at the nuclear periphery, restraining the transcriptional programme that commits preadipocytes to terminal differentiation (Lloyd et al., 2002; Capanni et al., 2005). Both reduced and excess LMNA expression impair adipogenesis, indicating that adipose tissue requires lamin A/C to sit within a narrow physiological range for normal fat-cell development (Capanni et al., 2005; Boguslavsky et al., 2006). Human data on LMNA transcript levels in adipose tissue remain sparse and inconsistent across depots and populations (Nadeau et al., 2010).

A separate line of evidence links the nuclear lamina to inflammation rather than only to differentiation. Lamin A/C is upregulated in adipose tissue macrophages during obesity, and macrophage-specific overexpression of lamin A/C is sufficient to activate nuclear factor kappa B (NF-κB) and drive transcription of interleukin-6 (IL-6), tumour necrosis

factor-alpha (TNF-α), and other pro-inflammatory genes, while myeloid-specific deletion of Lmna blunts obesity-induced adipose inflammation and improves insulin sensitivity in mice (Kim et al., 2018). Subcutaneous adipose tissue is itself a recognised source of circulating IL-6 (Mohamed-Ali et al., 1997), and IL-6 remains among the most consistently implicated cytokines in the pathogenesis of insulin resistance and T2DM (Donath and Shoelson, 2011). Whether adipose LMNA expression in humans relates to this inflammatory axis, and not only to adipocyte differentiation, has not to our knowledge been examined directly.

Femoral (thigh) subcutaneous LMNA expression did not differ significantly between diabetics and non-diabetics at the group level in this cohort; other adipose depots from the same cohort are being analysed separately and are not the subject of the present report. A null result at the group level, however, does not preclude a meaningful relationship between LMNA expression and the surrounding metabolic phenotype: two groups can have statistically indistinguishable mean expression while the underlying continuous trait still tracks systemic adiposity, lipid handling, or inflammation within each group. It is this trait-level relationship, rather than the group difference itself, that the present analysis was designed to test. Whether peripheral LMNA expression correlates with anthropometric, imaging-derived, and circulating inflammatory parameters, and whether any such relationship differs between diabetics and non-diabetics, has not previously been examined in this or any Asian Indian cohort.

We therefore undertook a correlation analysis of absolute femoral subcutaneous LMNA expression against anthropometric, lipid, glycaemic, adipocytokine, and DEXA/MRI-derived body-composition parameters in the same case-control cohort of Asian Indian adults with and without T2DM, hypothesising that the pattern of LMNA correlation with the metabolic and inflammatory phenotype would differ qualitatively between diabetics and non-diabetics, even in the absence of a group-level difference in mean expression.

MATERIAL AND METHODS

Study design and setting

This was a secondary correlation analysis of a hospital-based case-control cohort established in the Department of Biochemistry, in collaboration with the Department of Endocrinology, SMS Medical College and Attached Hospitals, Jaipur, Rajasthan, India. The study was approved by the Institutional Ethics Committee of SMS Medical College (Ref. No. 470/MC/EC/2022) and was conducted in accordance with the Declaration of Helsinki (2013 revision).

Participants

Eighty participants undergoing elective femur surgery were enrolled: 40 with T2DM diagnosed per American Diabetes Association 2022 criteria, and 40 non-diabetic controls with normal fasting plasma glucose, matched for age and sex. Exclusion criteria included type 1 diabetes, active infection or systemic inflammatory disease, malignancy, chronic hepatic or renal disease, and use of medications known to alter adipose tissue biology or insulin sensitivity (thiazolidinediones, systemic glucocorticoids). Written informed consent was obtained from all participants prior to enrolment. Venous blood was drawn pre-operatively on the morning of surgery, under fasting conditions, for both groups.

Anthropometric, biochemical, and body-composition assessment

Weight, height, waist and hip circumference, and a fasting lipid profile were recorded using standard clinical methods. Insulin resistance and β-cell secretory function were estimated using the Homeostatic Model Assessment indices, HOMA-IR and HOMA-β (Matthews et al., 1985). Whole-body composition (total body fat, fat mass index, android:gynoid ratio, trunk:leg and trunk:limb fat mass ratios) was assessed by dual-energy X-ray absorptiometry (DEXA), and abdominal visceral and subcutaneous adipose tissue area and hepatic fat fraction were assessed by 3-Tesla MRI at the L4–L5 vertebral level.

Adipocytokine and inflammatory marker panel

Serum adiponectin, leptin, IL-6, TNF-α, and high-sensitivity C-reactive protein (hsCRP) were measured by ELISA, and C-peptide by chemiluminescent immunoassay, on the same pre-operative fasting samples. These marker concentrations are used here as correlates of LMNA expression; the between-group comparison of these markers falls outside the scope of the present correlation analysis and is not repeated here.

Adipose tissue biopsy and quantitative RT-PCR

Femoral subcutaneous adipose tissue was collected intraoperatively and preserved for RNA extraction. Total RNA was extracted using the Qiagen RNeasy Mini Kit, reverse-transcribed using the QuantiNova RT Kit, and LMNA transcript levels were quantified by SYBR Green-based quantitative RT-PCR on a Rotor-Gene Q platform (Qiagen), with GAPDH as the reference gene. Relative and absolute expression values were derived using the $2^{-\Delta\Delta Ct}$ method (Livak and Schmittgen, 2001). The present analysis uses these same per-subject absolute LMNA expression values, here correlated against the phenotypic parameters listed above rather than compared between diagnostic groups.

Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk test. Pearson correlation coefficients between absolute LMNA expression and each anthropometric, lipid, glycaemic, adipocytokine, DEXA-derived, and MRI-derived parameter were calculated separately within the diabetic and non-diabetic groups (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA). A two-tailed P value <0.05 was considered nominally significant. Given the number of correlations tested (30 per group), a Bonferroni-corrected threshold of approximately $P<0.0017$ was also considered when interpreting

the robustness of individual findings; this is reported alongside nominal significance rather than used to exclude findings outright, given the exploratory, hypothesis-generating nature of this analysis.

RESULTS

Cohort characteristics

The diabetic group had significantly higher waist circumference, fasting glucose, HbA1c, and HOMA-IR, and lower HOMA-β, than the non-diabetic group (data not shown); the correlations below are presented independently of these between-group comparisons.

LMNA expression and its correlation with the metabolic and inflammatory phenotype

Absolute femoral subcutaneous LMNA expression did not differ significantly between diabetics and non-diabetics at the group level (geometric mean fold-change 0.81 in diabetics vs. 1.0 in non-diabetics, non-significant). Table 1 presents the correlation of this same per-subject expression value against the full panel of anthropometric, lipid, glycaemic, adipocytokine, DEXA-derived, and MRI-derived parameters, separately for each group.

In the diabetic group, no anthropometric, lipid, glycaemic, or DEXA-derived body-composition parameter correlated significantly with LMNA expression (all $P>0.1$). Three correlations reached significance: LMNA expression correlated strongly and positively with circulating IL-6 ($r=0.80$, $P<0.01$), and negatively with MRI-derived abdominal visceral fat ($r=-0.64$, $P=0.01$) and abdominal subcutaneous fat ($r=-0.67$, $P<0.01$).

In the non-diabetic group, the pattern was different and more extensive. LMNA expression correlated positively with hepatic fat fraction ($r=0.89$, $P<0.01$), trunk/limb fat mass ratio ($r=0.70$, $P<0.01$), HDL-C ($r=0.62$, $P<0.01$), VLDL-C ($r=0.49$, $P<0.01$), TNF-α ($r=0.41$, $P<0.01$), triglycerides ($r=0.33$, $P=0.01$), and the trunk:leg fat ratio ($r=0.32$, $P=0.01$), and negatively with total body fat percentage ($r=-0.29$, $P=0.02$) and fat mass/height² ($r=-0.25$, $P=0.04$). None of these parameters correlated significantly with LMNA expression in the diabetic group. Femoral adipocyte size did not correlate significantly with LMNA expression in either group (diabetic $r=-0.09$, $P=0.73$; non-diabetic $r=0.13$, $P=0.32$).

Figure 1 summarises, as a correlation profile, the parameters that reached nominal significance in at least one group, illustrating the divergent, and in several cases opposite-signed, pattern of LMNA correlation between diabetics and non-diabetics.

Table 1. Correlation of absolute femoral subcutaneous LMNA expression with anthropometric, lipid, glycaemic, adipocytokine, DEXA-derived, and MRI-derived parameters, by diabetes status

	Diabetic (n=40)		Non-diabetic (n=40)	
Parameter	**r**	**P**	**r**	**P**
Anthropometric				
Weight (kg)	-0.23	0.37	-0.03	0.81
BMI (kg/m²)	-0.37	0.15	-0.16	0.20
Waist circumference (cm)	-0.12	0.67	-0.04	0.75
Hip circumference (cm)	-0.39	0.12	0.01	0.94
Waist:hip ratio	0.14	0.59	-0.09	0.50
Lipid profile				
Total cholesterol (mg/dL)	-0.11	0.67	0.10	0.43
Triglycerides (mg/dL)	-0.17	0.50	0.33	0.01
HDL-C (mg/dL)	-0.12	0.64	0.62	<0.01
LDL-C (mg/dL)	-0.08	0.76	-0.06	0.69
VLDL-C (mg/dL)	-0.18	0.51	0.49	<0.01
Glycaemic / insulin resistance				
HOMA-β	-0.11	0.66	-0.09	0.52
HOMA-IR	-0.12	0.66	0.09	0.52
Fasting insulin (mU/L)	-0.08	0.76	0.06	0.69
Fasting glucose (mg/dL)	-0.14	0.61	0.12	0.38
HbA1c (%)	0.23	0.37	0.13	0.30
Adipocytokine / inflammatory panel				
C-peptide (ng/mL)	0.07	0.81	0.03	0.87
hsCRP (ng/mL)	-0.04	0.90	-0.04	0.81
Adiponectin (ng/mL)	-0.32	0.21	0.08	0.52

Leptin (pg/mL)	-0.13	0.64	0.01	0.96
IL-6 (pg/mL)	0.80	<0.01	-0.09	0.52
TNF-α (pg/mL)	-0.39	0.12	0.41	<0.01
DEXA body-fat distribution				
Total body fat (%)	-0.06	0.81	-0.29	0.02
Fat mass/height² (kg/m²)	-0.11	0.67	-0.25	0.04
Android:gynoid fat ratio	-0.09	0.76	-0.23	0.06
% fat trunk / % fat legs	0.04	0.87	0.32	0.01
Trunk/limb fat mass ratio	-0.04	0.87	0.70	<0.01
MRI-derived abdominal / hepatic fat				
Abdominal visceral fat (cm²)	-0.64	0.01	-0.11	0.38
Abdominal subcutaneous fat (cm²)	-0.67	<0.01	-0.18	0.15
Liver fat (%)	-0.24	0.37	0.89	<0.01
Adipocyte morphometry				
Femoral adipocyte size (µm²)	-0.09	0.73	0.13	0.32

r: Pearson correlation coefficient; values in bold denote P<0.05. HOMA-IR: homeostatic model assessment of insulin resistance; HOMA-β: homeostatic model assessment of β-cell function; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; TNF-α: tumour necrosis factor-alpha; DEXA: dual-energy X-ray absorptiometry; MRI: magnetic resonance imaging.

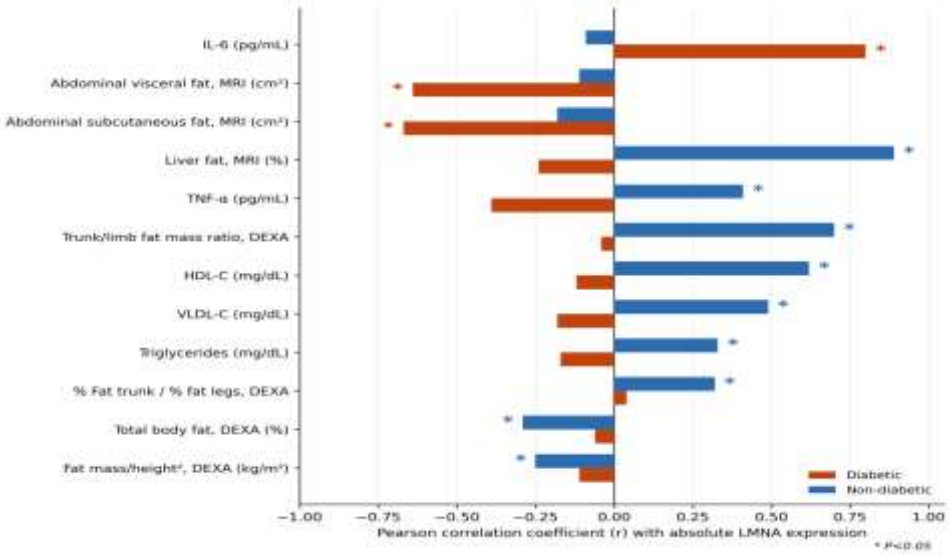

Figure 1. Correlation profile of absolute femoral LMNA expression with parameters reaching nominal significance (P<0.05) in at least one group. Bars show the Pearson correlation coefficient (r) in diabetics (red) and non-diabetics (blue); asterisks denote P<0.05 within that group. Note the divergent, and for several parameters opposite-signed, pattern between groups.

DISCUSSION

This analysis shows that femoral subcutaneous LMNA expression, despite showing no group-level difference between Asian Indian diabetics and non-diabetics, is not metabolically inert: its relationship with systemic adiposity, lipid handling, ectopic fat, and circulating inflammation is reorganised, rather than simply absent, in T2DM. In non-diabetics, LMNA expression rose in step with several markers of fat accumulation, including hepatic fat, trunk-predominant fat distribution on DEXA, and the atherogenic lipid parameters HDL-C, VLDL-C, and triglycerides, a pattern consistent with the proposed role of lamin A/C in physiologically restraining adipogenic capacity as the demand for lipid storage increases (Lloyd et al., 2002; Capanni et al., 2005; Boguslavsky et al., 2006). In diabetics, this coupling with adiposity and lipids was absent; in its place, LMNA expression correlated negatively with MRI-derived visceral and subcutaneous fat and, most strikingly, positively with circulating IL-6.

The IL-6 finding is, to our knowledge, the first report of a correlation between adipose LMNA expression and a circulating inflammatory cytokine in a human cohort. It is biologically plausible: macrophage-specific overexpression of lamin A/C activates NF-κB and drives IL-6 transcription directly, while myeloid deletion of Lmna blunts this response in mouse models of obesity-induced inflammation (Kim et al., 2018). A local shift toward a more pro-inflammatory, CD3-dominant

and CD163-depleted, macrophage profile in this same femoral depot in diabetics would be consistent with this pathway; testing that link directly would require matched per-subject immunohistochemistry and expression data, which were not available for the present analysis and remain a target for future work.

The negative correlation between LMNA expression and MRI-derived visceral and subcutaneous fat in diabetics, contrasted with essentially flat correlations in non-diabetics, is more difficult to reconcile with a simple restraint-of-adipogenesis model, in which higher LMNA would be expected to track with, not against, reduced fat storage capacity in a compartment other than the one biopsied. One possibility is that once the subcutaneous compartment's storage capacity is exceeded, a mechanism consistent with adipose tissue expandability and adiposopathy models (Virtue and Vidal-Puig, 2010; Bays, 2011), femoral LMNA regulation decouples from whole-body fat distribution altogether, since further peripheral adipogenic restraint no longer meaningfully affects where surplus lipid is deposited. This interpretation is speculative and cannot be confirmed by a cross-sectional correlation analysis.

The hepatic fat correlation is notable for its strength in non-diabetics ($r=0.89$) and its absence in diabetics ($r=-0.24$, non-significant). A possible explanation is a ceiling or saturation effect: once hepatic fat accumulation approaches a physiological ceiling, as may occur with longstanding T2DM, further variation in peripheral LMNA expression may no longer track incremental hepatic fat accumulation, whereas in non-diabetics, where hepatic fat is still within a narrower physiological range, the two may move together as part of a single, still-coordinated lipid-storage programme. This, too, is offered as a hypothesis rather than a demonstrated mechanism.

These findings illustrate that a gene can behave as a poor categorical marker of diabetes status while still functioning as a meaningful continuous correlate of physiology: despite showing no significant group-level difference in mean expression, femoral LMNA expression correlated strongly with several metabolic and inflammatory parameters within each group. Whether other adipose depots in this cohort show a comparable, or a distinct, pattern is being examined separately and lies outside the scope of the present analysis.

Limitations

This is a cross-sectional, exploratory correlation analysis and cannot establish causality or direction between LMNA expression, adiposity, and IL-6. Thirty correlations were tested per group; while the IL-6, visceral fat, and subcutaneous fat findings in diabetics, and the hepatic fat, trunk/limb ratio, and HDL-C findings in non-diabetics, remain significant under a conservative Bonferroni-corrected threshold, the weaker associations (triglycerides, VLDL-C, TNF-α, total body fat, fat mass/height², and the trunk:leg fat ratio in non-diabetics) should be considered nominal and hypothesis-generating rather than confirmed. Subgroup sizes (n=40 per group) limit power to detect smaller effect sizes. Adipocytokine and LMNA measurements were made at a single pre-operative time point, and no protein-level validation of lamin A/C was performed. We could not directly test the relationship between LMNA expression and local macrophage phenotype because per-subject CD163/CD3 counts were not available for this analysis. Finally, recruitment from an orthopaedic surgical cohort, and potential residual confounding by diabetes duration, glycaemic control, and medication use, are limitations of this cohort more broadly.

CONCLUSION

Femoral subcutaneous LMNA expression, despite showing no categorical difference by diabetes status, is a meaningful continuous correlate of the metabolic and inflammatory phenotype in Asian Indians, and this relationship is qualitatively reorganised in T2DM: physiological coupling with adiposity and lipid handling is lost, and a novel coupling with circulating IL-6 emerges. This possible mechanistic link is supported indirectly by previous studies in mice and human macrophages (Kim et al., 2018). However, direct studies measuring LMNA expression and macrophage characteristics in the same individuals are needed to confirm this relationship.

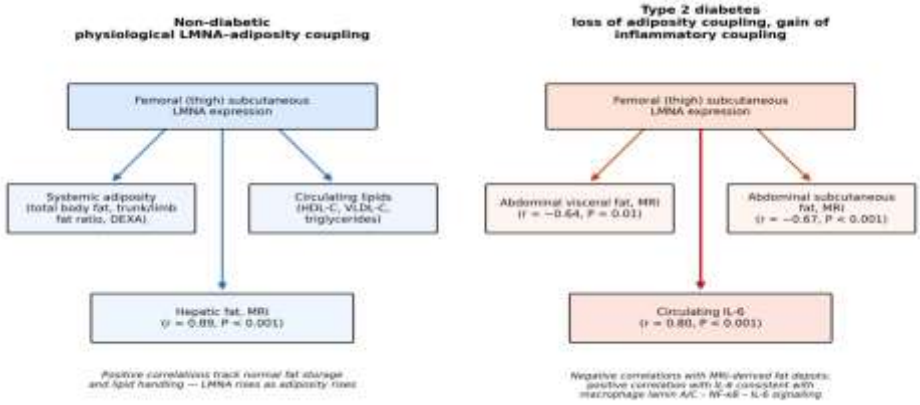

Figure 2. Proposed conceptual model of divergent LMNA coupling in non-diabetics versus type 2 diabetes. This schematic illustrates the pattern of correlation observed in Table 1 and Figure 1 and the mechanistic literature cited in the Discussion; it is not itself a data figure and does not depict individual-subject values.

Conflict of Interest

The authors declare no conflict of interest relevant to the content of this article.

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