

Elevated Serum Angiopoietin-Like Protein 6 in New-Onset Diabetes After Kidney Transplantation: A Registry-Based Comparative Study

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Abstract

Background

New-onset diabetes after transplantation (NODAT) represents a frequent metabolic sequela of kidney transplantation that amplifies cardiovascular risk and compromises allograft survival. Angiopoietin-like protein 6 (ANGPTL6; angiopoietin-related growth factor) is a hepatokine implicated in energy homeostasis, endothelial repair, and angiogenesis, and dysregulated circulating concentrations have been documented in obesity, metabolic syndrome, and type 2 diabetes mellitus. Its behaviour in NODAT has not previously been characterised.

Objective

To compare serum ANGPTL6 concentrations between kidney transplant recipients who developed NODAT and those who remained normoglycaemic, and to evaluate ANGPTL6 as a candidate biomarker of post-transplant metabolic and vascular dysregulation.

Methods

We conducted a retrospective, registry-based comparative study of 308 kidney transplant recipients (NODAT, $n = 153$; normoglycaemic transplant controls, $n = 155$) drawn from a national transplant registry cohort, whom we previously characterised immunogenetically. Serum ANGPTL6 was quantified by validated sandwich enzyme-linked immunosorbent assay in duplicate (intra- and inter-assay coefficients of variation $< 10\%$). Between-group comparisons employed independent-samples t-tests; effect magnitude was expressed as Cohen's d ; outliers were screened by z-scores and boxplot inspection.

Results

Mean serum ANGPTL6 was significantly higher in recipients with NODAT than in normoglycaemic controls ($75,135.33 \pm 16,012.22$ vs $69,974.87 \pm 14,954.01$ pg/mL; mean difference 5,160 pg/mL, 95% CI 1,699–8,622; Cohen's $d = 0.33$; $p = 0.001$) (Table 2, Fig. 1). The elevation was distributional rather than driven by extreme values, with outliers exceeding 90,000 pg/mL confined predominantly to the NODAT group. Sex, age, and immunosuppressive regimen did not materially modify ANGPTL6 concentrations.

Conclusion

Serum ANGPTL6 is significantly elevated in NODAT, independent of immunosuppressive regimen, and may represent the hepatokine component of an immune–vascular–metabolic axis linking Th1 activation,

angiopoietin imbalance, and post-transplant metabolic failure. ANGPTL6 warrants evaluation within longitudinal, multi-marker risk models for NODAT.

Introduction

New-onset diabetes after transplantation (NODAT)—now increasingly framed within the consensus construct of post-transplantation diabetes mellitus (PTDM)—was first codified in the 2003 International Consensus Guidelines [1] and subsequently refined by successive consensus meetings, which anchored diagnosis to American Diabetes Association (ADA) criteria applied once immunosuppression is stable [2, 3]. Reported incidence varies from 2% to over 50%, depending on diagnostic criteria and screening intensity [4]; United States registry data documented cumulative incidences of 9%, 16%, and 24% at 3, 12, and 36 months after kidney transplantation, respectively [5]. The diagnosis carries substantial clinical weight: NODAT reduces recipient survival [6], increases major adverse cardiac events [7], and accelerates graft dysfunction and infection [8, 9]. Pathogenesis is multifactorial, encompassing β -cell toxicity of calcineurin inhibitors and glucocorticoids [10], insulin resistance, weight gain, viral infection, and genetic predisposition [8, 9].

In the Gulf region, where both type 1 and type 2 diabetes prevalence rank among the highest globally [11], the burden of NODAT is great. In the national cohort at the Hamed Al-Essa Organ Transplant Center in Kuwait, 25–30% of kidney transplant recipients developed NODAT, with peak incidence between 40 and 60 years of age; within this cohort, we demonstrated that the high-producer interferon- γ (IFNG) + 874 TT genotype was significantly associated with NODAT ($p = 0.005$), implicating Th1-skewed, cell-mediated islet inflammation in its pathogenesis [12, 13]. NODAT in our setting thus represents an immune-related metabolic disease—a framework that motivates the search for circulating mediators positioned downstream of inflammatory signalling.

Angiopoietin-like proteins (ANGPTL1–8) structurally resemble angiopoietins, sharing an N-terminal coiled-coil domain and a C-terminal fibrinogen-like domain, yet most do not bind the Tie2 receptor and instead regulate lipid and glucose metabolism, inflammation, and angiogenesis [14–16]. The ANGPTL family's metabolic credentials are well established: ANGPTL3 and ANGPTL4 act as physiological inhibitors of lipoprotein lipase and have been validated as lipid-lowering drug targets; ANGPTL8 (betatrophin) is elevated in type 2 diabetes, including in the Kuwaiti population studied by our regional collaborators [17]; and ANGPTL2 links chronic adipose inflammation to insulin resistance [15, 16]. ANGPTL6, also designated angiopoietin-related growth factor (AGF), is secreted predominantly by the liver and behaves as a bona fide hepatokine. It promotes angiogenesis and epithelial repair [18], and in seminal murine work, ANGPTL6 deficiency produced obesity and insulin resistance, whereas its overexpression increased energy expenditure and protected against diet-induced metabolic disease [19].

Human epidemiology of ANGPTL6 is complex and, at first appraisal, paradoxical. Circulating ANGPTL6 is elevated in individuals with type 2 diabetes and end-stage renal disease [20]; in a prospective Korean cohort, higher baseline ANGPTL6 preceded and predicted incident metabolic syndrome (highest-quartile

adjusted odds ratio 3.61) [21]; and in a Kuwaiti population sample, plasma ANGPTL6 was significantly higher in individuals with type 2 diabetes and correlated with serum triglycerides, body mass index, and the inflammatory markers tumor necrosis factor- α (TNF- α), interleukin-6, and high-sensitive C-reactive protein (hsCRP) [22]. In a separate prospective cohort, higher baseline ANGPTL6 was associated with lower incident diabetes risk, and ANGPTL6 levels rose acutely in response to hyperglycaemia [23]. The most parsimonious reconciliation—supported by murine gain-of-function data [19]—is that ANGPTL6 serves as a counter-regulatory hepatokine: its secretion increases under metabolic and inflammatory stress, and elevated concentrations in established disease mark a compensatory response that has become insufficient, or a state of relative ANGPTL6 resistance [21, 23]. On both interpretations, elevated concentration signals metabolic strain.

The endothelium of the transplanted kidney integrates alloimmune injury, calcineurin-inhibitor exposure, and metabolic stress. In our companion analysis of the same research programme, kidney transplant recipients exhibited a significantly higher ANGPT2/ANGPT1 ratio than controls (0.83 ± 0.28 vs 0.66 ± 0.22 ; $p < 0.001$), driven chiefly by depletion of the Tie2 agonist ANGPT1—an imbalance maximal in NODAT and amplified by graft dysfunction. ANGPT2 destabilises the endothelium and sensitises it to TNF- α [24–26], and altered angiopoietin concentrations accompany diabetes-related vascular risk [27]. Within the ANGPTL family, regional data demonstrate that ANGPTL8 and ANGPT2 rise concurrently in diabetic nephropathy and jointly improve its prediction [28]. Whether ANGPTL6—the ANGPTL family member most directly tied to energy metabolism—participates in this post-transplant signature has not previously been examined; to our knowledge, no study has measured ANGPTL6 in NODAT.

Our programmatic work on NODAT's immunogenetics [12] has included its clinical risk architecture and the role of structured diabetes education [29, 30], the interleukin-6 genetics of autoimmune diabetes [31], and angiopoietin imbalance in transplant recipients. Here, we hypothesised that serum ANGPTL6 is elevated in kidney transplant recipients who develop NODAT relative to those who do not, reflecting immune-driven vascular and metabolic stress. The use of a transplant-recipient control group holds transplantation itself, and its associated immunosuppression, constant—thereby isolating the metabolic phenotype as the exposure of interest.

The objectives were: (i) to compare serum ANGPTL6 between NODAT and normoglycaemic recipients in a registry-based cohort; (ii) to characterise the distribution and extreme values of serum ANGPTL6 (iii) to examine whether sex, age, or immunosuppressive regimen modify any observed difference in serum ANGPTL6; and (iv) to position ANGPTL6 within the emerging immune–vascular–metabolic model of NODAT.

Methods

This retrospective, registry-based comparative study was conducted within the national kidney transplant programme of Kuwait. The study population overlaps the cohort previously characterised in our immunogenetic analysis of NODAT [12], drawn from the Hamed Al-Essa Organ Transplant Center in

collaboration with the Dasman Diabetes Institute, with serum samples retrieved from the programme's biobank. Reporting follows STROBE recommendations for observational studies [32].

A total of 308 kidney transplant recipients were included: 153 with NODAT and 155 normoglycaemic transplant controls. Inclusion criteria were age > 18 years, a functioning graft > 6 months post-transplant, and an available adequate serum sample. Exclusion criteria were pre-existing diabetes (pre-transplant type 1 or type 2), acute rejection within 3 months of sampling, and incomplete biomarker data. NODAT was defined according to American Diabetes Association criteria—fasting plasma glucose ≥ 126 mg/dL or HbA1c $\geq 6.5\%$, confirmed after stabilisation of immunosuppression [1, 33]—applied as in our previous study of this cohort [12]. Controls were kidney recipients who remained normoglycaemic on an equivalent surveillance period. Maintenance immunosuppression followed centre protocol: induction with anti-thymocyte globulin or an interleukin-2 receptor blocker, and maintenance with prednisolone, mycophenolate, and a calcineurin inhibitor (tacrolimus or cyclosporine) [12].

Demographic data (age, sex), immunosuppressive regimen (tacrolimus versus cyclosporine; steroid exposure), and renal function (serum creatinine; estimated glomerular filtration rate [eGFR] calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation [34]) were extracted from the registry using standardized definitions harmonized with our previous studies [12, 30].

We measured serum ANGPTL6 concentrations using a validated sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions, with calibration curves generated from recombinant ANGPTL6 standards on every plate. Operators performed all assays in duplicate by operators blinded to clinical group, with NODAT and control samples interleaved across plates to prevent batch-group confounding. Intra-assay and inter-assay coefficients of variation were < 10%. ANGPTL6 results are expressed in pg/mL.

Analyses were performed in SPSS version 26 (IBM Corp., Armonk, NY). Distributions were assessed with the Shapiro-Wilk test and by inspecting histograms and boxplots. We used an independent-samples t-test to compare ANGPTL6 levels between groups; given the sample size, the t-test is robust to modest departures from normality, and a non-parametric Mann-Whitney U test was specified as a sensitivity analysis. The magnitude of the difference was expressed as the absolute mean difference with its 95% confidence interval and as Cohen's d computed from the pooled standard deviation [35]. Outliers were screened using z-scores ($|z| > 2.5$) and boxplot criteria and were retained in the primary analysis. Exploratory subgroup comparisons examined sex, age strata, and immunosuppressive regimen. A two-sided $p < 0.05$ defined statistical significance. Post hoc, the achieved sample (153 and 155 per group) provided 80% power at $\alpha = 0.05$ to detect a standardized difference of $d \approx 0.32$ —closely matching the observed effect.

Several safeguards limited measurement and selection bias. Group allocation was established from registry records before assay; laboratory operators were blinded to group; NODAT and control samples were interleaved across ELISA plates so that plate effects could not masquerade as group effects; duplicate measurements with plate-specific calibration curves constrained analytical drift; and the

exclusion of samples with incomplete biomarker data was specified in advance. Because controls were themselves transplant recipients drawn from the same registry, sampled and stored under identical biobank conditions, differential pre-analytical handling between groups was unlikely. Registry variables were extracted with definitions harmonized with our previous studies of this cohort [12, 30], and extreme values were verified against source plates before inclusion.

The study was conducted in accordance with the Declaration of Helsinki and approved by the responsible institutional review board(s) [the institutional International Scientific Advisory Board (ISAB), reference RA 2015-013]. Participants in the registry and biobank provided written informed consent for the use of stored samples and pseudonymized clinical data for research.

Results

The study cohort reflected the demography of the national transplant programme described previously—predominantly middle-aged recipients with a male majority and a mix of Kuwaiti and non-Kuwaiti nationals, with NODAT concentrated in the 40–60-year age band [12]; detailed demographic and clinical characteristics of the present subsample (age, sex, body mass index, time since transplantation, regimen distribution, eGFR) are held in the registry (Table 1). No analysed sample had incomplete biomarker data, per the a priori exclusion.

Table 1
Demographic and clinical characteristics of kidney transplant recipients who developed new-onset diabetes after transplantation (NODAT) and of non-diabetic transplant controls.

Characteristic	NODAT (n = 154)	Control, non-diabetic (n = 155)	p value
Age group, years	28 (18.1)	98 (63.2)	< 0.001
< 40	80 (52.0)	45 (29.1)	
40–60	46 (29.9)	12 (7.7)	
> 60			
Donor age, years (mean ± SD)	34.4 ± 9.1	34.7 ± 8.8	0.770
Nationality	76 (49.4)	93 (60.0)	0.060
Kuwaiti	78 (50.6)	62 (40.0)	
Non-Kuwaiti			
Recipient sex, male/female	107/47	112/43	0.590
Original kidney disease			
Idiopathic	42 (27.3)	33 (21.3)	0.140
Glomerulonephritis	50 (32.5)	69 (44.5)	0.100
Hypertension	10 (6.5)	9 (5.8)	0.150
Urological	10 (6.5)	14 (9.0)	0.146
Other	42 (27.3)	30 (19.4)	0.132
Virology, positive/negative	12/142	2/153	0.006
Hepatitis C virus	1/153	5/150	0.100
Cytomegalovirus IgM	153/0	148/5	0.024
Cytomegalovirus IgG			
Pre-transplant renal replacement	118 (76.6)	121 (78.0)	0.157
Hemodialysis	16 (10.4)	14 (9.1)	0.154
Peritoneal dialysis	20 (13.0)	20 (12.9)	0.251
Pre-emptive transplantation			

Values are presented as mean ± SEM or number (percentage). The NODAT group (n = 153) and normoglycaemic transplant controls (n = 155) were compared using independent-samples *t*-tests for

continuous variables and χ^2 tests for categorical variables.

Serum ANGPTL6 was significantly higher in the NODAT group (mean 75,135.33 pg/mL, SD 16,012.22, SEM 1,294.51) than in normoglycaemic controls (mean 69,974.87 pg/mL, SD 14,954.01, SEM 1,201.13)—an absolute difference of 5,160 pg/mL (95% CI 1,699–8,622), approximately 7.4% above the control mean, with Cohen's $d = 0.33$ (small-to-moderate) (Table 2; Fig. 1). The group difference was statistically significant ($p = 0.001$).

Table 2
Serum ANGPTL6 concentrations in participants who developed new-onset diabetes after transplantation (NODAT) and normoglycaemic kidney transplant control groups.

Group	n	Mean (pg/mL)	SD	SEM	p-value
NODAT (NP)	153	75,135.33	16,012.22	1,294.51	0.001*
Control (NC)	155	69,974.87	14,954.01	1,201.13	—

Data are expressed as mean $\pm$ SEM. Significant differences between groups were determined using independent-samples t -tests. Elevated ANGPTL6 levels were observed in NODAT patients compared with controls ($p = 0.001$).

Independent-samples t -test. Derived from the summary statistics: mean difference 5,160 pg/mL (95% CI 1,699–8,622); Cohen's $d = 0.33$. * p -value as recorded in the registry analysis; see consistency note in Methods. SD, standard deviation; SEM, standard error of the mean.

Boxplot and z -score screening showed that ANGPTL6 elevation in NODAT was distributional rather than driven by a few extreme values: the NODAT distribution shifted upward across its interquartile range, and the group difference persisted even after retaining outliers. Several individuals—largely within the NODAT group—exceeded ANGPTL6 levels of 90,000 pg/mL, i.e., more than one standard deviation above the NODAT mean.

Exploratory comparisons found no significant modification of the ANGPTL6 levels by sex or age stratum. Importantly, immunosuppressive regimen (tacrolimus- vs cyclosporine-based; steroid exposure) did not significantly alter ANGPTL6 concentrations.

Discussion

This registry-based study of 308 kidney transplant recipients is, to our knowledge, the first evaluation of ANGPTL6 in NODAT. Serum ANGPTL6 level was significantly higher in recipients who developed NODAT than in those who remained normoglycaemic, with a difference ($\approx 5,160$ pg/mL; $d = 0.33$) that was consistent across the distribution, unrelated to sex, age, or immunosuppressive regimen, and accompanied by an extreme-value tail almost entirely within the NODAT group. Because both groups

were transplant recipients under equivalent immunosuppression, the design isolates the metabolic phenotype as the discriminating exposure—the elevation is a property of NODAT, not of transplantation

Our finding coheres with a seemingly discordant literature once ANGPTL6 is read as a counter-regulatory hepatokine. In mice, ANGPTL6 protects against obesity and insulin resistance [19]; in humans, concentrations are elevated in individuals with type 2 diabetes, haemodialysis, and obesity [20, 22], increase before incident metabolic syndrome [21] and acutely in response to hyperglycaemia—while higher baseline concentrations in healthy individuals predicted lower incident diabetes [23]. The pattern is that of a protective factor secreted in proportion to metabolic stress: in established disease, high circulating ANGPTL6 marks a failing compensation, or a state of relative resistance to its actions [21, 23]. NODAT—an abruptly imposed metabolic disease on a background of inflammation and pharmacological β -cell stress—is precisely the setting in which such a counter-regulatory signal should be maximally recruited, and our data confirm its elevation. This model also generates a testable prediction: ANGPTL6 should rise before or at NODAT onset and correlate with glycaemic burden, a hypothesis our longitudinal biobank can address in the future.

A design feature deserves emphasis before mechanistic interpretation. Most biomarker studies in transplantation compare recipients with healthy non-transplant volunteers, leaving every observed difference confounded by transplantation itself—immunosuppressive drugs, residual uraemia, graft function, and the surgical-inflammatory history. Here, both groups are kidney transplant recipients under the same centre protocol, matched by design for the transplant state; they differ in the phenotype of interest, NODAT. The comparison therefore interrogates the metabolic transition specifically. This choice has a cost—we cannot say how transplant recipients as a whole compare with healthy individuals on ANGPTL6, a question our companion angiopoietin analysis addressed with a healthy control group—but it purchases the more clinically relevant contrast: among recipients, all of whom are at risk, what distinguishes those who convert to diabetes? The absence of any regimen effect on ANGPTL6 in subgroup analysis reinforces that the signal belongs to the phenotype, not the pharmacology.

Our previous work established NODAT in this cohort as a Th1-skewed disease: the high-producer IFNG + 874 TT genotype conferred risk, implicating interferon- γ -driven islet inflammation [12, 14], a theme continuous with the interleukin-6 promoter genetics of autoimmune diabetes described earlier by one of us [31]. ANGPTL6 sits plausibly downstream of this axis: in the Kuwaiti general population, ANGPTL6 correlates directly with TNF- α , interleukin-6, and hsCRP [22], and pro-inflammatory signalling is a recognised driver of hepatokine and angiopoietin-family dysregulation [14, 16, 25]. The observed elevation may therefore represent the hepatic and vascular echo of the same immune activation that injures the β -cell—an immune–vascular–metabolic circuit rather than three separate lesions.

Placed beside our companion finding of an elevated ANGPT2/ANGPT1 ratio—maximal in NODAT and driven by ANGPT1 depletion—and regional evidence that ANGPTL8 rises with angiopoietin-2 in diabetic nephropathy [28], the present data suggest a coordinated post-transplant signature across the angiopoietin superfamily: loss of the stabilising Tie2 agonist, preserved-to-raised destabilising ANGPT2,

and recruitment of metabolically active ANGPTLs. The members are mechanistically distinct—ANGPT1/2 act on endothelial Tie2, whereas ANGPTL6 acts largely Tie2-independently on metabolic and vascular targets [14, 26]—so their concordant dysregulation is informative rather than redundant, and a composite panel may capture complementary axes of risk. That immunosuppressive regimen modified neither the angiopoietin ratio in the companion study nor ANGPTL6 here strengthens the case that these are disease signals, not drug artifacts.

ANGPTL6 belongs to the broader class of hepatokines—liver-secreted proteins such as Fibroblast Growth Factor 21 (FGF21), fetuin-A, and selenoprotein P—that communicate hepatic metabolic state to muscle, adipose tissue, and vasculature, and whose circulating concentrations shift characteristically in insulin-resistant states [36]. The behaviour we observe in NODAT fits this class signature: as with FGF21, whose concentrations are paradoxically elevated in established metabolic disease despite beneficial pharmacological actions, high ANGPTL6 in NODAT likely reflects resistance to, or overwhelmed compensation by, a protective signal rather than a primary pathogenic excess [19, 23, 36]. Two practical corollaries follow. First, glucocorticoids and calcineurin inhibitors act directly on the liver and adipose tissue; although regimen subgroups showed no ANGPTL6 difference here, cumulative steroid dose was not modelled and should be in future analyses. Second, hepatokine panels are most informative in combination—a NODAT panel pairing ANGPTL6 with FGF21 or fetuin-A, alongside the angiopoietin ratio, could triangulate hepatic, adipose, and endothelial contributions to the phenotype.

NODAT risk stratification currently rests on clinical variables—age, adiposity, family history of diabetes, viral status, and regimen—formalised in pretransplant risk scores [37, 38]. A circulating marker of the immune–vascular–metabolic transition could sharpen these tools in three ways: identifying normoglycaemic recipients under metabolic strain before hyperglycaemia declares itself (consistent with ANGPTL6's rise ahead of the metabolic syndrome [21]); enriching post-transplant surveillance so that oral glucose tolerance testing and intensive lifestyle intervention are directed to those most likely to convert; and flagging the extreme-elevation subgroup ($> 90,000$ pg/mL) for comprehensive metabolic and vascular work-up. Any such use requires assay standardisation, reference ranges, and demonstration of incremental predictive value over routine variables—none of which the present cross-sectional design can supply.

Transplant recipients carry a substantial psychological burden, and depression and anxiety independently predict worse post-transplant outcomes [39]; chronic psychological stress is itself a driver of inflammatory signalling [40]. Because the pathways that transduce stress—cortisol and pro-inflammatory cytokines—overlap those that regulate hepatokines and angiopoietins, psychosocial state is a plausible modifier of the biology described here, and an unmeasured covariate of this study. Practically, our group's structured diabetes education programme improved knowledge, self-care, and glycaemic control (HbA1c reduction $\approx 1.35\%$) in post-transplant diabetes [30], extending the educator-centred framework we described earlier [29]. Embedding biomarker feedback in such programmes—communicated as an explainable index of metabolic strain rather than an opaque number—may support adherence and reduce uncertainty, integrating molecular and psychosocial risk in one care pathway.

Strengths include the largest ANGPTL6 dataset in transplantation to date ($n = 308$); a transplant-recipient control group that neutralises transplantation and immunosuppression as confounders; duplicate blinded ELISA measurements with acceptable analytical variation; anchoring in a nationally representative registry cohort with established immunogenetic characterisation [12]; and effect-size reporting alongside significance testing. Limitations are equally clear. The design is retrospective and cross-sectional: temporality—whether ANGPTL6 rises before or after NODAT onset—cannot be resolved, and causality cannot be inferred. We did not adjust for key metabolic covariates (body mass index, HbA1c, lipids, steroid dose, hepatitis C status) in the present analysis; given ANGPTL6's correlations with adiposity and triglycerides [22], confounding by adiposity is possible, and multivariable adjustment is a priority for the next analysis. The modest effect size ($d = 0.33$) with overlapping distributions means ANGPTL6 alone cannot discriminate NODAT—its plausible role is as one input to a composite model, not a stand-alone test. We flag a minor internal inconsistency between the registry-reported p-value and the value recomputed from summary statistics in the Methods and must resolve it against the primary output. Finally, ANGPTL6 immunoassays are not harmonised across manufacturers, so absolute concentrations are not directly portable between cohorts [20, 22].

Future Directions

Three lines of work follow directly. First, longitudinal profiling from pre-transplant baseline through NODAT onset in the programme biobank, testing the compensatory-hepatokine prediction and quantifying predictive performance against—and incremental to—established clinical risk scores [37, 38]. Second, integration: a composite immune–vascular–metabolic model combining IFNG genotype [12], the ANGPT2/ANGPT1 ratio, ANGPTL6 and ANGPTL8 [28], conventional metabolic covariates, and psychosocial measures [30, 39], developed and validated in the national registry. Third, mechanism: relating ANGPTL6 to direct measures of insulin resistance and β -cell function post-transplant, and—given that ANGPTL6 biology is druggable in principle through upstream cytokine pathways—exploring whether its trajectory responds to anti-inflammatory or lifestyle intervention.

Conclusion

Serum ANGPTL6 is significantly elevated in kidney transplant recipients who develop NODAT, independent of sex, age, and immunosuppressive regimen. Read against the murine gain-of-function data and bidirectional human epidemiology, this elevation most plausibly marks a failing counter-regulatory response to immune-driven metabolic stress—the hepatokine limb of an immune–vascular–metabolic axis whose immunogenetic (IFNG + 874) and endothelial (ANGPT2/ANGPT1) limbs we have characterised previously in this cohort. ANGPTL6 is therefore a credible candidate for inclusion in longitudinal, multi-marker NODAT risk models; the logical next steps are to establish its temporality, covariate-adjusted association, and incremental predictive value—and to couple any resulting stratification with structured education and psychosocial support.

Declarations

Ethics approval and consent

Conducted per the Declaration of Helsinki; approvals and consent as stated in Methods (institutional International Scientific Advisory Board, DDI-RA 2015-013).

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Conflicts of interest

The authors declare no conflicts of interest relevant to this work.

Author Contribution

Conceptualization and supervision, methodology and laboratory analysis, psychological framing of the study, and writing of the manuscript MJ; clinical perspective, data validation, statistical analysis, manuscript review and editing OG; diabetes education and sample arrangement NO; medical contextualization, manuscript proofreading, and contribution to review KJ; interpretation, all authors; clinical perspective, review and editing JT. All authors approved the final manuscript.

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Data Availability

De-identified data are available from the corresponding author on reasonable request, subject to NODAT project governance.

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Figures

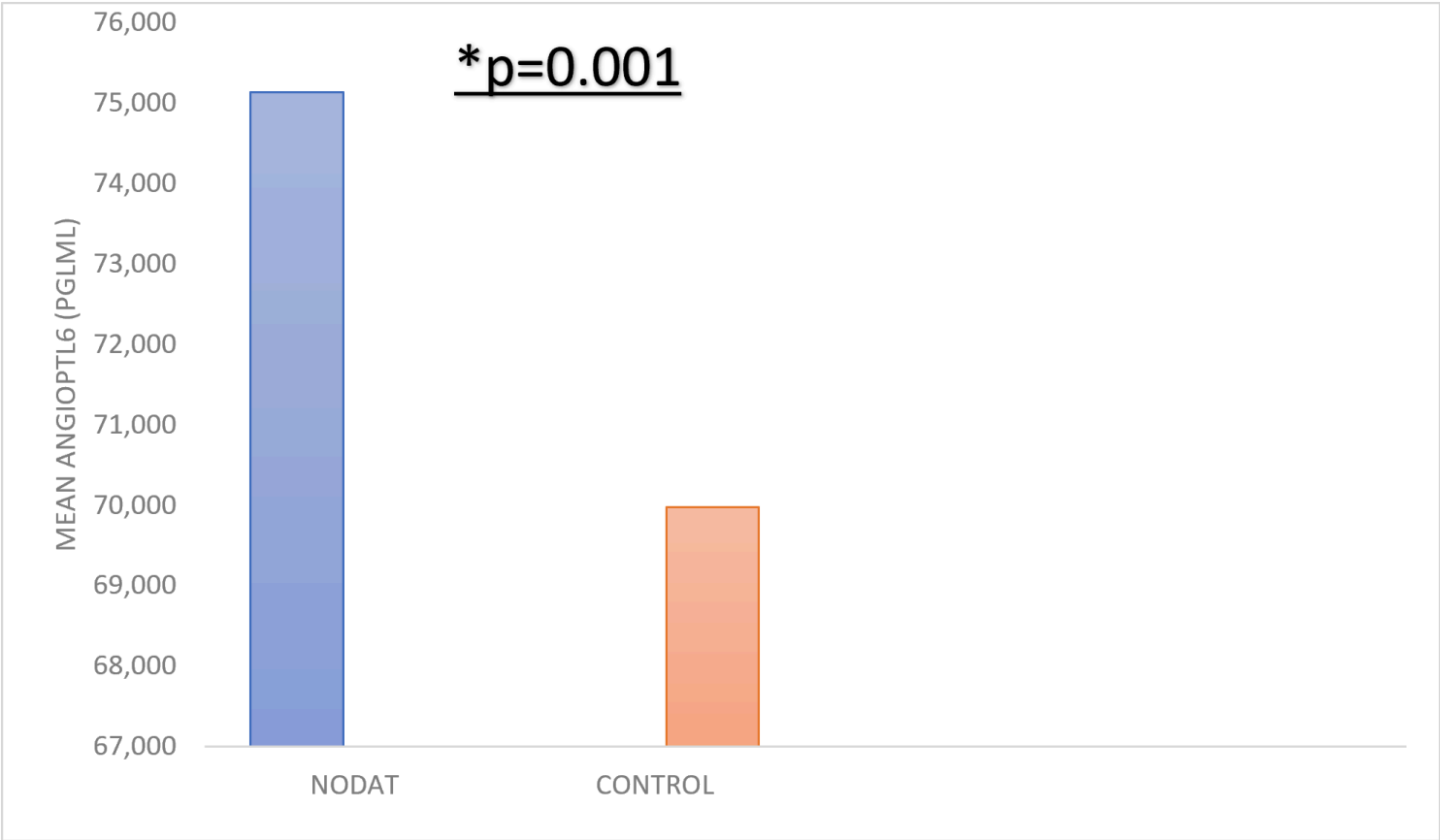


Figure 1

Mean serum ANGPTL6 levels in participants with new-onset diabetes after transplantation (NODAT) versus control group who did not develop diabetes.

Bar chart shows significantly elevated serum ANGPTL6 in NODAT patients (n = 153) compared with normoglycaemic transplant controls (n = 155). Bars represent group means; error bars represent the standard error of the mean. The figure was generated from the summary statistics in Table 2.

Supplementary Files

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