**Supplementary Appendix**

 This appendix has been provided by the authors to give readers additional information about their work.

 Supplement to: Gunaid AA, Al-Kebsi MM, Bamashmus MA, Al-Akily AA, Al-Radaei AN. Clinical Phenotyping of Newly-Diagnosed Type 2 Diabetes in Yemen.

 **Table-S1: General characteristics of newly-diagnosed patients with type 2 diabetes by sex**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter | Sex | Mean | SD | 95% CI | Median | IQR | p-value |
| Age (year) | M | 45.69 | 11.29 | 44.47 - 46.99 | 46.00 | 37.00, 53.00 | 0.001 |
| F | 49.01 | 10.39 | 47.49 - 50.48 | 50.00 | 41.00, 55.00 |
| Duration of DM(days) | M | 28.00 | 30.00 | 25.00 – 31.00 | 14.00 | 7.00, 35.00 | 0.955 |
| F | 28.00 | 34.00 | 23.00 – 33.00 | 14.00 | 0.00, 42.00 |
| BMI (kg/m2) | M | 27.63 | 4.71 | 27.05 - 28.10 | 27.00 | 24.30, 29.80 | 0.002 |
| F | 29.07 | 5.20 | 28.38 - 29.90 | 28.60 | 25.40, 32.00 |
| WC (cm) | M | 99.75 | 11.00 | 98.39 - 100.83 | 99.00 | 93.00, 106.00 | 0.944 |
| F | 99.74 | 12.08 | 98.13 - 101.64 | 100.00 | 91.00, 106.00 |
| LAP (cm.mmol/l) | M | 69.86 | 38.82 | 65.35 – 74.37 | 60.00 | 40.00, 88.00 | 0.056 |
| F | 78.02 | 43.89 | 71.58 – 84.46 | 69.00 | 42.00, 104.00 |
| SBP (mm Hg) | M | 128.43 | 17.76 | 126.52 - 130.50 | 130.00 | 120.00, 140.00 | 0.008 |
| F | 133.01 | 19.62 | 130.55 - 136.21 | 130.00 | 120.00, 140.00 |
| DBP (mm Hg) | M | 79.88 | 9.42 | 78.86 - 80.97 | 80.00 | 70.00, 82.00 | 0.629 |
| F | 80.29 | 8.58 | 79.22 - 81.69 | 80.00 | 70.00, 85.00 |
| HbA1c (%) | M | 9.79 | 2.30 | 9.52 - 10.03 | 9.50 | 7.80, 11.50 | 0.283 |
| F | 9.57 | 2.16 | 9.24 - 9.87 | 9.10 | 7.80, 11.00 |
| HbA1c (mmo/mol) | M | 83.48 | 24.98 | 80.55 - 86.11 | 80.00 | 62.00, 102.00 | 0.313 |
| F | 81.19 | 23.66 | 77.55 - 84.41 | 76.00 | 62.00, 97.00 |
| eAG (mmol/l) | M | 13.00 | 3.60 | 12.60 – 13.40 | 12.50 | 9.80, 15.70 | 0.307 |
| F | 12.70 | 3.50 | 12.10 – 13.10 | 11.90 | 9.80, 14.90 |
| e-GFR(ml/min/1.73m2) | M | 85.33 | 16.78 | 83.43 - 87.18 | 85.00 | 74.00, 95.00 | 0.029 |
| F | 82.13 | 14.07 | 80.11 - 84.21 | 81.00 | 74.00, 93.00 |
| u-ACR (mg/g) | M | 58.77 | 67.69 | 51.48 - 66.64 | 33.00 | 18.00, 76.00 | 0.480 |
| F | 59.87 | 71.18 | 49.62 - 70.38 | 38.00 | 20.00, 73.00 |
| TC (mmol/l) | M | 5.06 | 1.18 | 4.92 - 5.19 | 5.00 | 4.30, 5.66 | 0.158 |
| F | 5.21 | 1.18 | 5.04 - 5.39 | 5.00 | 4.32, 5.91 |
| HDL (mmol/l) | M | 1.06 | .21 | 1.04 - 1.08 | 1.00 | 0.94, 1.20 | <0.001 |
| F | 1.15 | .23 | 1.11 - 1.18 | 1.10 | 1.00, 1.30 |
| TG (mmol/l) | M | 2.43 | 1.93 | 2.22 - 2.65 | 2.00 | 1.32, 3.00 | 0.011 |
| F | 2.04 | 1.64 | 1.81 - 2.29 | 2.00 | 1.00, 2.15 |
| LDL (mmol/l) | M | 3.01 | 1.02 | 2.90 – 3.12 | 3.00 | 2.38, 3.60 | 0.028 |
| F | 3.22 | 1.00 | 3.07 – 3.35 | 3.20 | 2.47, 3.90 |
| TC/HDL | M | 4.93 | 1.64 | 4.75 - 5.11 | 4.60 | 3.90, 5.60 | 0.210 |
| F | 4.67 | 1.24 | 4.50 - 4.87 | 4.50 | 3.80, 5.40 |
| TG/HDL | M | 2.47 | 2.34 | 2.21 - 2.73 | 1.90 | 1.20, 2.90 | <0.001 |
| F | 1.89 | 1.49 | 1.69 - 2.12 | 1.60 | 1.00, 2.20 |
| Non-HDL-C(mmol/l) | M | 4.00 | 1.18 | 3.87 - 4.13 | 3.90 | 3.30, 4.60 | 0.612 |
| F | 4.06 | 1.16 | 3.90 - 4.24 | 4.00 | 3.30, 4.70 |

Figure S1-A - HOMA-β by clusters (phenotypes) of T2D

Figure S1-B - HOMA-S by clusters (phenotypes) of T2D

Figure S1-C - HOMA-IR by clusters (phenotypes) of T2D

Figure S1- HOMA modeling of type 2 diabetes by phenotypes: Median (25, 75 IQR): the highest median HOMA2-β (Fig.S1-A) is that of cluster 1 and the lowest of cluster 2. The highest median HOMA2-S (Fig.S1-B) is that of cluster 2 and the lowest is that of cluster1. The higher median HOMA-IR (Fig.S1-C) is that of cluster 1 and 3 and the lower is that of cluster 2.

**Table-S2: HOMA modeling comparison between control subjects and patient clusters**

| **Variables** | **Control Subjects** | **Cluster-1: High insulin resistance and high beta cell function group** | **Cluster-2: Low insulin resistance and low beta cell function group** | **Cluster-3: High insulin resistance and low beta cell function group** | **p-value** |
| --- | --- | --- | --- | --- | --- |
| Individuals (*n*): | 165 | 126 | 218 | 156 |  |
| HOMA-%β |  |  |  |  |  |
|  Mean (SD) | 147.6 (53.7) | 95 (54.5) | 25.9 (18.3) | 34.6 (21.7) | <0.001 |
|  Median (IQR) | 138.4 (106.4, 176.4) | 78.3 (60.5, 113) | 22.3 (11.9, 34.8) | 30 (16.5, 48.3) |  |
| HOMA-%S |  |  |  |  |  |
|  Mean (SD) | 63.4 (28.9) | 35.4 (13.6) | 81.2 (33.9) | 41.5 (15.9) | <0.001 |
|  Median (IQR) | 55.9 (41.8, 79.3) | 34.3 (25.4, 40.7) | 76 (59.8, 94.3) | 40.9 (31.2, 51.3) |  |
| HOMA-IR |  |  |  |  |  |
|  Mean (SD) | 2.9 (1.2) | 7.2 (4.0) | 3.4 (1.3) | 6.5 (3.0) | <0.001 |
|  Median (IQR) | 2.7 (1.9, 3.7) | 6.3 (4.5, 8.8) | 3.3 (2.3, 4.3) | 6.4 (4.3, 7.8) |  |

**Table S3-: Association between NAFLD and other variables (n=500)**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Yes (n= 359) | No (n= 141) |  |
| freq. | (%) | Mean (SD) | Median (IQR) | freq. | (%) | Mean (SD) | Median (IQR) | ***p*-value** |
| Age |  |  |  | 46.25 (10.40) | 46.00 (39.00 , 54.00) |  |  | 48.67 (12.47) | 48.00 (40.0, 56.00) | 0.042 |
| Gender |  |  |  |  |  |  |  |  |  |  |
|  | Male | 216 | (69.0) |  |  | 97 | (31.0) |  |  | 0.073 |
|  | Female | 143 | (76.5) |  |  | 44 | (23.5) |  |  |  |
| HbA1c % |  |  | 9.72 (2.23) | 9.40 (7.90 ,11.30) |  |  | 9.68 (2.29) | 9.50 (7.60, 11.30) | 0.865 |
| HbA1c mm/m |  |  | 82.78 (24.42) | 79.0 (63.00, 100.0) |  |  | 82.22 (24.9) | 80.0 (60.0, 100.0) | 0.819 |
| BMI |  |  |  | 29.41 (4.86) | 28.9 (26.00, 31.90) |  |  | 25.00 (24.90) | 24.80 (22.80, 27.10) | <0.001 |
| WC |  |  |  | 102.54 (11.06) | 101.00 (95.00, 108.00) |  |  | 92.63 (8.92) | 93.0 (86.0, 99.0) | <0.001 |
| LAP |  |  |  | 81.00(42.62) | 74.25 (45.00, 105.40) |  |  | 53.13 (28.22) | 46.90 (30.60, 68.00) | 0.003 |
| HOMA-β |  |  | 50.23 (47.23) | 37.00 (17.80, 67.60) |  |  | 35.23 (28.22) | 28.30 (15.00, 49.40) | <0.001 |
| HOMA-S |  |  | 47.61 (22.43) | 43.90 (31.20, 62.00) |  |  | 81.88 (41.10) | 75.20 (51.80, 104.50) | <0.001 |
| HOMA-IR |  |  | 5.94 (3.25) | 5.30 (3.60, 7.40) |  |  | 3.69 (2.54) | 3.10 (2.20, 4.40) | <0.001 |
| QUICKI |  |  |  | 0.30 (0.02) | 0.30 (0.29, 0.32) |  |  | 0.32 (0.03) | 0.32 (0.31, 0.34) | <0.001 |
| TG |  |  |  | 2.38 (1.89) | 2.00 (1.21, 3.00) |  |  | 2.03 (1.66) | 1.96 (1.00, 2.00) | 0.041 |
| SBP |  |  |  | 131.12 (18.59) | 130.00 (120.00, 140.00) |  |  | 127.66 (18.42) | 125.0 (118.0, 140.0) | 0.061 |
| DBP |  |  |  | 80.50 (9.08) | 80.00 (70.00, 86.00) |  |  | 78.85 (9.12) | 80.0 (70.0, 80.0) | 0.069 |
| MetS  |  |  |  |  |  |  |  |  |  | <0.001 |
|  | Positive | 265 | (80.5) |  |  | 64 | (19.5) |  |  |  |
|  | Negative | 94 | (55.0) |  |  | 77 | (45.0) |  |  |  |
| [BMI ≥ 30+TG ≥ 2.3] | 42  | (95.5) |  |  | 2.0  | (4.5) |  |  | <0.001 |
| [BMI < 30/ TG < 2.3] | 317 | (69.5) |  |  | 139 | (30.5) |  |  |  |
| Clusters of T2D: |  |  |  |  |  |  |  |  |  |
|  | Cluster 1 | 110 | (87.3) |  |  | 16 | (12.7) |  |  | <0.001 |
|  | Cluster 2 | 119 | (54.6) |  |  | 99 | (45.4) |  |  |  |
|  | Cluster 3 | 130 | (83.3) |  |  | 26 | (16.7) |  |  |  |

*Abbreviation: HbA1c;* Glycohemoglobin (%, mmol/mol); *BMI:* body mass index (kg/m2); *WC:* waist circumference; *LAP:* Lipid Accumulation Product (cm.mmol/l); *HOMA2* (Homeostasis Model Assessment)- %β (beta-cell function), %S (insulin sensitivity), IR (insulin resistance); *QUICKI:* quantitative insulin sensitivity check index; *TG:* serum triglyceride concentration (mmol/l); *SBP* (systolic blood pressure); *DBP* (diastolic blood pressure); *MetS* (metabolic syndrome).

 **Table-S4: First degree family history of diabetes by phenotype of DM**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| FH (Family History) | Cluster 1 | Cluster 2 | Cluster 3 |  Chi-square  | *p*-value |
| FH - |  |  |  |  |  |  |
|  | Ob | 49 | 112 | 67 | 7.10 | 0.131 |
| Ex | 57.5 | 99.4 | 71.1 |
| Ob-Ex | -8.5 | **+12.6** | -4.1 |
| FH+ |  |  |  |  |
|  | Ob | 61 | 91 | 74 |
| Ex | 57.0 | 98.5 | 70.5 |
| Ob-Ex  | **+4.0** | -7.5 | **+3.5** |
| FH++ |  |  |  |  |
|  | Ob | 16 | 15 | 15 |
| Ex | 11.6 | 20.1 | 14.4 |
| Ob-Ex | **+4.4** | -5.1 | 0.6 |
| Total | 126 | 218 | 156 |

*Abbreviation:* ***FH-* :** *No first-degree relatives with adult-onset T2D;* ***FH +* :** *Family history of diabetes in one or both parents, single or ≥ 2 siblings, or single-sibling and single parent;* ***FH++* :** *Family history of diabetes in a combination of ≥ 3siblings and parents, i.e. ≥ 2 siblings + single parent or single sibling and both parents.*

Although the association was not significant (χ2 = 7.1,*p* = 0.131), yet most of the higher observed than expected (Ob-Ex) frequencies in cluster (1) came from the presence of diabetes in parent(s), sibling(s) or single parent & sibling [FH+] (+4.0) and a combination of ≥ 3 siblings and parents [FH++] (+ 4.4). In cluster (3), the higher observed than expected (Ob-Ex) frequencies came from the presence of diabetes in [FH+] only (+ 3.5). Conversely, in cluster (2), the higher observed than expected (Ob-Ex) frequencies (+12.6) came from the non-diabetic relatives (FH-).