Supplementary Material

Supplementary Figure Legends

Figure S1. Identification of T2DM mice model with obesity or non-obesity. (A) Roadmap of mouse model building (T2DM with obesity). (B) Growth curve of T2DM mice with obesity. (n = 10-30) (C) Blood glucose of T2DM mice with obesity. (n = 10-30) (D) Serum insulin content of T2DM mice with obesity. (n = 6) (E) HOMO-IR of T2DM mice with obesity. (n = 6) (F) ITT of T2DM mice with obesity in the 4th week of the disease course. (n = 6) (G) Roadmap of mouse model building (T2DM with non-obesity). (H) Growth curve of T2DM mice with non-obesity. (n = 9-50) (I) Blood glucose of T2DM mice with non-obesity. (n = 9-38) (J) Serum insulin content of T2DM mice with non-obesity. (n = 6) (K) HOMO-IR of T2DM mice with non-obesity. (n = 6) (L) GTT of T2DM mice with non-obesity in the 4th week of the disease course. (n = 6) (M) ITT of T2DM mice with non-obesity in the 24th week of the disease course. (n = 6) (N) HE staining of islet tissues in the 24th and 36th week of the disease course (Scale bar = 50 µm). Data are expressed as mean ± SD. (*, p<0.05; **, p<0.01; ***, p<0.001.).

Figure S2. The heart rate and cardiac diastolic function of obese and non-obese T2DM mice. (A) Heart rate of obese mice in the 24th week of the disease course. (B) Mitral valve rheography of obese mice in the 24th week of the disease course. (C) E/A ratio of obese mice in the 24th week of the disease course. (D) Aortic ejection time of obese mice in the 24th week of the disease course. (E) Isovolumetric contraction time of obese mice in the 24th week of the disease course. (F) Isovolumetric relaxation time of obese mice in the 24th week of the disease course. (G) Heart rate of non-obese mice in the 36th week of the disease course before and after anesthesia. (H) Mitral valve rheography of non-obese mice in the 24th and 36th week of the disease course. (I) E/A ratio of non-obese mice in the 24th and 36th week of the disease course. (J) Aortic ejection time of non-obese mice in the 24th and 36th week of the disease course. (K) Isovolumetric contraction time of non-obese mice in the 24th and 36th week of the disease course. (L) Isovolumetric relaxation time of non-obese mice in the 24th and 36th week of the disease course. Data are expressed as mean ± SD. (*, p<0.05; **, p<0.01; ***, p<0.001. n = 6-10 for each group).

Figure S3. Serum lipids of obese and non-obese T2DM mice. (A) Serum FFAs content of obese T2DM mice. (B) Serum TG content of obese T2DM mice. (C) Serum TC content of obese T2DM mice. (D) Serum LDL content of obese T2DM mice. (E) Serum HDL content of obese T2DM mice. (F) Serum FFAs content of non-obese T2DM mice. (G) Serum TG content of non-obese T2DM mice. (H) Serum TC content of non-obese T2DM mice. (I) Serum LDL content of non-obese T2DM mice. (J) Serum HDL content of non-obese T2DM mice. Data are expressed as mean ± SD. (*, p<0.05; **, p<0.01; ***, p<0.001. n = 6 for each group).

Figure S4. Western blot results of proteins related to insulin resistance and glycogen synthesis in heart tissues from T2DM mice. (A) Western blot images of proteins related to Akt pathway in hearts from obese T2DM mice. (B) Relative quantification based on the panel A. (C) Western blot images of proteins related to Akt pathway in hearts tissues from non-obese T2DM mice. (D) Relative quantification based on the panel C. Data are expressed as mean ± SD. (*, p<0.05; **, p<0.01; ***, p<0.001. n = 3 for each group)
Figure S5. Western blot results of proteins related to oxidative stress and apoptosis in heart tissues from obese T2DM mice. (A) Western blot images of proteins related to oxidative stress and apoptosis in heart tissues from obese T2DM mice. (B) Relative quantification based on the results of panel A. Data are expressed as mean ± SD. (*, p<0.05; **, p<0.01; ***, p<0.001. n = 3 for each group)

Figure S6. Western blot results of proteins related to oxidative stress and apoptosis in heart tissues from non-obese T2DM mice. (A) Western blot images of proteins related to oxidative stress and apoptosis in heart tissues from non-obese T2DM mice. (B) Relative quantification based on the results of panel A. Data are expressed as mean ± SD. (*, p<0.05; **, p<0.01; ***, p<0.001. n = 3 for each group)

Figure S7. The summary picture of the results in T2DM mice. The summary picture showing the differences of cardiac function and molecular mechanism in hearts of T2DM mice with obesity or non-obesity through the disease course.

Figure S8. Competency in medical knowledge and translational outlook. Obese T2DM exhibits more severe and sustained lipotoxicity compared to non-obese T2DM. Non-obese T2DM exhibits a significant decrease in antioxidant capacity in the event of systolic dysfunction compared to obese T2DM. Obese T2DM is more prone to cardiac systolic dysfunction due to different cardiac energy metabolism and oxidative stress adaptations in T2DM with obese and non-obese. Different BMI can be used as a basis for judging energy intervention or antioxidant therapy.
Figure S1
Figure S2
Figure S3
Figure S4
Figure S5
Figure S6
Type 2 Diabetes Mellitus

Obesity

Non-obesity

FFAs uptake(CD36,FABP3)
FFAs oxidation(PPARα,CPT1α)
Glucose uptake(GLUT4)
Lipolysis(ATGL)
Antioxidation(Nrf2,HO-1,NQO1)

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Glucose uptake(GLUT4)
Lipolysis(ATGL)
Antioxidation(Nrf2,HO-1,NQO1)

Baseline
4 weeks
12 weeks
24 weeks
36 weeks
Compensatory
Heart failure

Figure S7
Figure S8
Table S1. The information of antibodies.

| Antibodies | Manufacture and item NO. | Application |
|------------|--------------------------|-------------|
| CD31       | Abcam(ab28364)           | Immunofluorescence |
| PPARα      | Abcam(ab8934)            | Western blotting |
| CD36       | Sigma(b104094)           | Western blotting |
| FABP3      | Cell signaling technology(14780S) | Western blotting |
| FATP4      | Sigma(SAB2102194)        | Western blotting |
| CPT1α      | Abcam(ab128568)          | Western blotting |
| ATGL       | Cell signaling technology(2439S) | Western blotting, IHC |
| GLUT4      | Cell signaling technology(2213S) | Western blotting |
| p-Akt(T308)| Cell signaling technology (13038S) | Western blotting |
| p-Akt(S73) | Cell signaling technology (4060S) | Western blotting |
| Akt        | Cell signaling technology (46915S) | Western blotting |
| p-GSK-3β   | Cell signaling technology (5558S) | Western blotting, IHC |
| GSK-3β     | Cell signaling technology (12456S) | Western blotting |
| Nrf2       | Cell signaling technology (12721S) | Western blotting |
| HO-1       | Cell signaling technology (70081S) | Western blotting, IHC |
| NQO1       | Abcam (ab28947)          | Western blotting |
| Histone H3 | Cell signaling technology (4499S) | Western blotting |
| (Cleave)Caspase3 | Cell signaling technology (9915T) | Western blotting |
| Bax        | Beyotime (AB026)         | Western blotting |
| Bcl-2      | Beyotime (AB112)         | Western blotting |
| β-actin    | Cell signaling technology (3700S) | Western blotting |
| FABP3      | Proteintech (10676-1-AP)  | IHC |
| CPT-1α     | Proteintech (15184-1-AP)  | IHC |
| NQO1       | Proteintech (11451-1-AP)  | IHC |
Table S2. Primers for qPCR.

| Genes  | Primers                                                                 |
|--------|-------------------------------------------------------------------------|
| Mouse ANP | F: 5′-GCTTCAGGCATATTGGAGCA-3′                                           |
|         | R: 5′-TCTTCAGAGGAGTGTGGACCT-3′                                          |
| Mouse BNP | F: 5′-ATGGATCTCTGGAAGTGTGTCC-3′                                         |
|         | R: 5′-GCAGCTTGGATATGTGTGCACC-3′                                         |
| Mouse Acadvl | F: 5′-ATCAGGTGTCCCATACCCA-3′                                           |
|          | R: 5′-TCTTGAGTCCCCGCAAAGT-3′                                            |
| Mouse Acsl1 | F: 5′-AACGAGGCAAGAAGTGTGGG-3′                                          |
|           | R: 5′-TGGTGAGTGGATCCATGTCC-3′                                           |
| Mouse Acadm | F: 5′-AGGATGACGGAGCGAGCCAAT-3′                                          |
|            | R: 5′-ATCTGGGTAGACGCGTTGCA-3′                                           |
| Mouse Cpt1β | F: 5′-CGTTCAGGCATGTACATG-3′                                              |
|           | R: 5′-AGAGCCAGACCTTGGAAGAAG-3′                                           |
| Mouse Acaa2 | F: 5′-TCAACAGGCTCTGGAAGTCTCT-3′                                        |
|           | R: 5′-TGCCCAACAAAGCACCTT-3′                                              |
| Mouse Fabp3 | F: 5′-CTGGACGGAGGAAGAACCTCAT-3′                                         |
|           | R: 5′-AGGGGAACCCATGGGAGG-3′                                               |
| Mouse CD36 | F: 5′-GATGAGCATAAGCTTGATGTC-3′                                          |
|           | R: 5′-CACCACCGGAGCAATCCCA-3′                                              |
| Mouse GAPDH | F: 5′-TGCGACTTCAACAGCAACTC-3′                                          |
|            | R: 5′-GCCTCTGGCAGTGATGCC-3′                                               |
Table S3. The information of donors.

| No. | Type                        | Gender | Age (Years) | Abdominal fat thickness (cm) | Heart weight (g) |
|-----|-----------------------------|--------|-------------|------------------------------|------------------|
| 1   | T2DM with obesity           | Male   | 43          | 3.5                          | 380              |
| 2   | T2DM with obesity           | Male   | 55          | 3.4                          | 500              |
| 3   |                             | Female | 68          | 4                            | 350              |
| 4   |                             | Male   | 49          | 11                           | 700              |
| 5   |                             | Female | 45          | 3                            | 400              |
| 6   |                             | Female | 63          | 3                            | 450              |
| 7   | Healthy population (Control group for T2DM with obesity) | Male | 41 | 1.5 | 350 |
| 8   |                             | Male   | 55          | 1.5                          | 350              |
| 9   |                             | Female | 68          | 2.1                          | 300              |
| 10  |                             | Male   | 51          | 1.2                          | 420              |
| 11  |                             | Female | 44          | 2.7                          | 300              |
| 12  |                             | Female | 64          | 1.8                          | 350              |
| 13  |                             | Male   | 64          | 1.5                          | 500              |
| 14  |                             | Male   | 50          | 1.2                          | 600              |
| 15  |                             | Female | 68          | 1.4                          | 400              |
| 16  |                             | Female | 66          | 1                            | 350              |
| 17  |                             | Male   | 41          | 1                            | 380              |
| 18  |                             | Male   | 72          | 2                            | 520              |
| 19  |                             | Male   | 49          | 1.3                          | 300              |
| 20  |                             | Female | 70          | 2.4                          | 440              |
| 21  |                             | Male   | 64          | 2                            | 400              |
| 22  |                             | Male   | 51          | 1.2                          | 420              |
| 23  |                             | Male   | 68          | 2.1                          | 300              |
| 24  |                             | Female | 64          | 1.8                          | 350              |
| 25  | Healthy population (Control group for T2DM with non-obesity) | Female | 68 | 1.6 | 300 |