**Suppl 3.** Cell culture and *in vitro* GDF15 secretion assay

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| Cell culture | Human hepatocyte cell line HepG2 cells were cultured in Dulbecco’s modified Eagle’s medium containing 25 mM glucose (D5796; Sigma, USA) supplemented with 10% fetal bovine serum, 100 units/ml penicillin, and 100 µg/ml streptomycin in a humidified incubator at 37℃ containing 5% CO2. They were exposed to imeglimin (SML2401; Sigma-Aldrich, Australia) before analysis. |
| *In vitro* GDF15 Secretion Assay | HepG2 cells were incubated with or without 1 µg/ml imeglimin or 2 µg/mL imeglimin for 48 hours. The medium was centrifuged at 500 x g, 4oC for 5 minutes, **and** the supernatant was collected for GDF15 measurement. The HepG2 cells were lysed for total protein measurement. The GDF15 in the supernatant was measured with Quantikine Human GDF15 kit (DGD150; R&D System, USA). The total protein was measured with Protein Assay BCA kit (06385-00; Nacalai Tesque, USA). |

GDF15, growth differentiation factor 15.