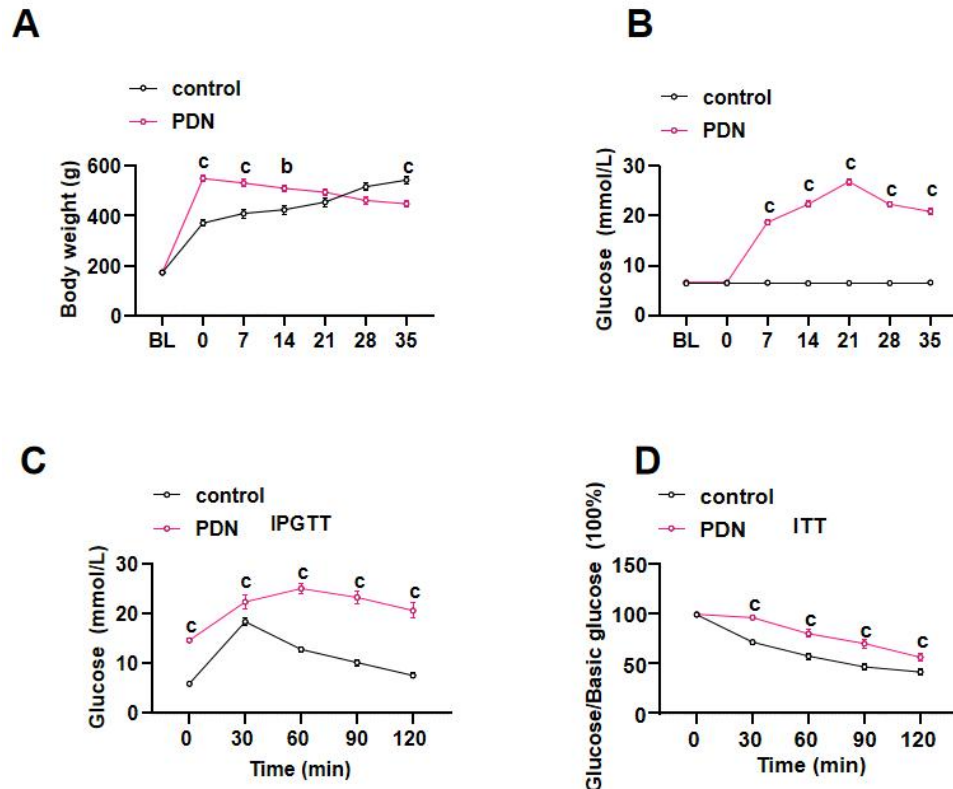
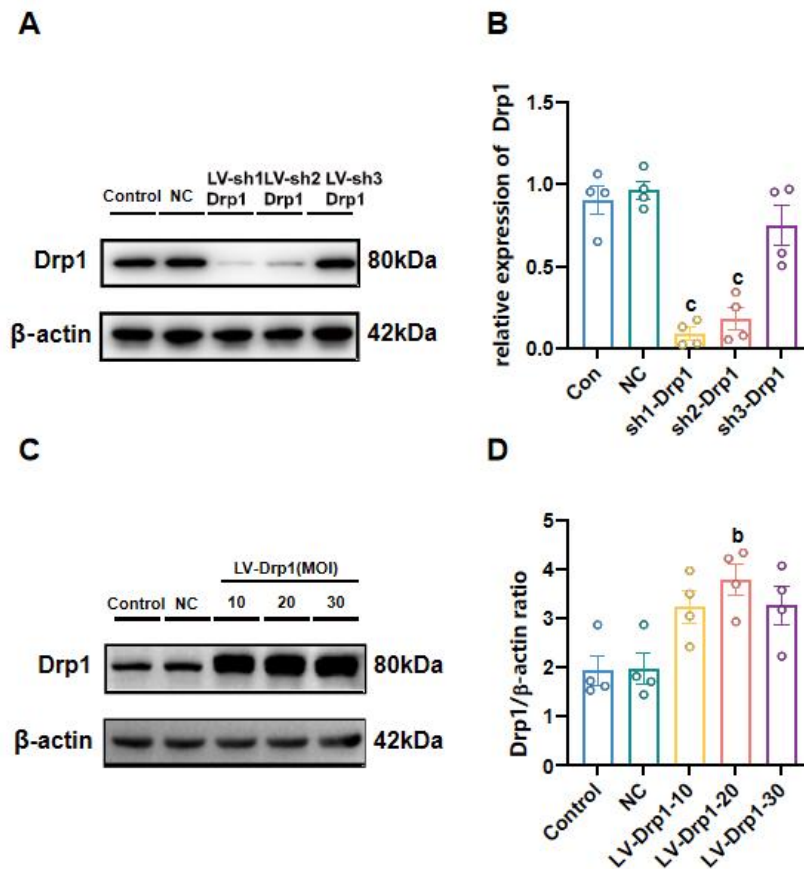




Supplementary Figure 1 A PDN rat model induced by high-fat diet (HFD) and low-dose streptozotocin (STZ). A: Changes in body weight of rats. B: Changes in blood glucose levels after intraperitoneal carnosine injection. C: Intraperitoneal glucose tolerance test (IPGTT) conducted on rats at day 7 after STZ injection. D: Insulin tolerance test (ITT) conducted on rats at day 14 after STZ injection. ^b $P < 0.01$, ^c $P < 0.001$ compared with the control group; Two-way ANOVA with Sidak's multiple comparisons test for A-D; $n = 11$.



Supplementary Figure 2 Validation of Drp1 knockdown and overexpression viruses. A-B: WB of protein expression following Drp1 knockdown with LV-shDrp1, including representative electrophoresis bands and relative expression levels. C-D: WB of protein expression following Drp1 overexpression with LV-Drp1, including representative electrophoresis bands and relative expression levels. ^b $P < 0.01$, ^c $P < 0.001$ compared with the control group; One-way ANOVA with Tukey's multiple comparisons test for B and D; $n = 4$.

Supplementary Table 1 The up-regulated metabolites with top 10 variable importance in projection scores between the painful diabetic neuropathy and control groups in positive mode

Metabolite	VIP	FC (PDN/CON)	<i>P</i>	Trend
Sorbitol	3.54	1.2305	8.05E-06	Up
Pyridoxine	3.3665	1.2756	0.001564	Up
Puerarin	3.2294	1.2218	2.07E-06	Up
L- (+)-Arginine	3.2072	1.2094	3.50E-05	Up
Cyproheptadine	3.1349	1.2082	0.000402	Up
Methyl-3-[(2-nitrobenzoyl) amino] benzoate	3.0603	1.2174	0.001833	Up
Gentiobiose	3.0568	1.1584	0.000217	Up
3-Hydroxysebacic acid	2.865	1.1884	0.01375	Up
D- (-)-Erythrose	2.7812	1.1105	2.59E-05	Up
D (-)-Threose	2.7306	1.1023	1.41E-05	Up

VIP, variable importance in projection; FC, fold change; CON, Control.

Supplementary Table 2 The down-regulated metabolites with top 10 variable importance in projection scores between the painful diabetic neuropathy and control groups in positive mode

Metabolite	VIP	FC (PDN/CON)	<i>P</i>	Trend
DG (24:3)	3.749	0.5782	1.15E-05	Down
Chalcone	3.5195	0.7491	0.004853	Down
Famciclovir	3.3247	0.8012	0.001406	Down
Mesoridazine	3.0053	0.8444	0.000113	Down
DG (38:4)	2.9972	0.6817	0.001729	Down
Liquiritigenin	2.9881	0.7918	0.02728	Down
Apramycin	2.7936	0.8716	2.74E-06	Down
HexCer (18:02O/22:0)	2.7389	0.6777	0.01935	Down
Hydratoperidin	2.7256	0.8625	0.01083	Down
Homoveratrylamine	2.6276	0.8617	0.005952	Down

VIP, variable importance in projection; FC, fold change.

Supplementary Table 3 The up-regulated metabolites with top 10 variable importance in projection scores between the painful diabetic neuropathy and control groups in negative mode

Metabolite	VIP	FC (PDN/CON)	<i>P</i>	Trend
Mannose	3.5114	1.2063	1.26E-06	Up
Ethyl-beta-glucuronide	3.5015	1.2832	4.34E-05	Up
Maltitol	3.1902	1.2332	6.61E-07	Up
FA (19:22O)	3.1127	1.9215	0.001608	Up
Picrotin	2.9189	1.1551	6.37E-06	Up
Methyl-beta-galactopyranoside	2.8996	1.2127	0.000838	Up
Ononin	2.896	1.2252	0.002376	Up
Psicose	2.8645	1.1273	9.85E-06	Up
Urocanic acid	2.7787	1.1196	1.67E-06	Up
N-Tris (hydroxymethyl) methyl-2-aminoethanesulfonic acid	2.7706	1.1759	0.01106	Up

VIP, variable importance in projection; FC, fold change.

Supplementary Table 4 The down-regulated metabolites with top 10 variable importance in projection scores between the painful diabetic neuropathy and control groups in negative mode

Metabolite	VIP	FC (PDN/CON)	<i>P</i>	Trend
Cochlioquinone A	3.4917	0.7964	0.001055	Down
13-HpOTrE (r)	2.8812	0.8355	0.000168	Down
Apigenin	2.6261	0.8546	0.006009	Down
[6]-Gingerol	2.5361	0.9063	0.003777	Down
Gly-Tyr	2.4177	0.8957	0.000177	Down
Nitrazepam	2.3804	0.8866	0.000229	Down
Carnosine	2.2934	0.9077	0.004705	Down
PC (18:0)	2.2908	0.7757	0.004682	Down
Homoarginine	2.1409	0.9019	0.01402	Down
Chrysin	2.0784	0.9118	0.00456	Down

VIP, variable importance in projection; FC, fold change.